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EPIDEMIOLOGY OF ENTERITIS IN YOUNG CHILDREN[1]

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THE ætiology and epidemiology of gastro-enteritis in young children have been studied extensively in the last few years, and considerable efforts have been made to restrict the spread of the infection in hospitals and children's homes. The most comprehensive study of this kind in Australia has been summarized by Mackerras and Mackerras (1949). The observations described in the present paper are a direct continuation of these studies, and, as Mackerras and Mackerras fully trace the different ways by which infections spread, it seems superfluous to repeat their discussions here. One fact, however, should be mentioned. The epidemic of salmonellosis, which formed the chief object of study during the period 1947 to 1949, declined in intensity, until *Salmonella bovis-morbificans* disappeared almost completely during 1951. The predominant organisms during the period under study were *Shigella sonnei* and *Escherichia coli* O 111 (α *coli*).

Sh. sonnei was introduced into the Brisbane area in November, 1949, and infections with *E. coli* O 111 seemed to be very uncommon until recently. Although sporadic infections might have occurred without our knowledge before April, 1951, when regular typing of *E. coli* strains commenced, no major institutional outbreaks occurred prior to November, 1951. Similarly *E. coli* O 55 (β *coli*) was not found in a child before June, 1952, although many thousands of Escherichia strains had been typed.

The literature reveals that most studies are concerned with the progress of established epidemics, and devotes little attention to the problem of introduction and primary spread of the infection.

One of the first papers to consider these problems more closely has been published recently by Rogers (1951), who traced the introduction of pathogenic types of *E. coli* into hospitals and hospital wards. In another paper (1951) Rogers and Koegler focused attention on aerogenous spread.

These papers show a curious disregard of the epidemiological significance of the adult hospital population. However, it has been stressed by other authors and committees that adult personnel are a potential source of infection. McKinlay (1937) reported an infection by a Salmonella-like organism in four babies. A nurse was found excreting the organism in large numbers, and seemed the probable cause of the outbreak. Cummings (1947), in an attempt to control neonatal diarrhœa, examined monthly nose, throat and stool specimens from nursery personnel and from mothers on admission to hospital. The Medical Research Council (1951), in its description of procedure to be adopted after the occurrence of infection, stressed that nursing staff, including food handlers, should be bacteriologically examined when dysentery, paratyphoid, typhoid or food poisoning occurs in a ward. Felsen, Weil and Wolarsky (1950) have recommended frequent examinations of all food handlers in hospitals and of nurses in children's wards. These recommendations do not seem to have been widely carried out.

Australian authors, as a rule, have placed due emphasis on the importance of adult carriers. Mackerras and Mackerras (1949) examined 228 adults in the maternity hospital series and found seven Salmonella carriers.

[1] Received for publication August 21, 1952.

Rubbo (1948, 1952) made the carrier (whether adult or child) one of the main sources of infection. Both studies were concerned mainly, although not exclusively, with institutional infections in hospitals. Personal experience has shown that, despite the fact that great energy is being expended in preventive measures directed against inanimate objects and possible animal vectors, no serious attempts are made to find and exclude carriers among patients and staff.

The chief infections which were studied in the present investigation—enteritis caused by *Sh. sonnei* and *E. coli* O 111—have usually been more acute than the majority of Salmonella infections encountered. This, together with the fact that both have only recently been causing major outbreaks in Brisbane, makes them particularly useful for the study of the main epidemiological pathways by which infections enter institutions, and which are decisive in the question of primary spread or subsidence. Discussion of these questions will be the main object of this paper.

We are very grateful to the authorities in charge of the various institutions for the opportunities they have given us.

Material and Methods

The hospitals and other institutions which submitted to examinations were visited at least once a week, and cultures were taken from all children who had been newly admitted and from all children who had shown signs of digestive disorder during the past week. In one of the homes, a group of children was examined regularly every week to obtain a picture of changes in the intestinal flora.

Specimens were taken by rectal swabbing as described previously, and the bacteriological methods used for the characterization of Salmonella and Shigella followed the routine which had been in use in this Institute for some time (Fison and Singer, 1950).

The examination of the strains of *E. coli* which were isolated from the fæces followed, with minor modifications, the techniques described by Vahlne (1945).

When typing was restricted to a search for *E coli* O 111 and *E. coli* O 55, at least four colonies of *E. coli* were transferred to sectors of a plate of 0·1% glucose-heart infusion agar, and the resulting growth was tested after four to six hours by slide agglutination against rabbit immune serum containing both "O" and "L" antibodies. If agglutination occurred, the type of the strain was verified next day by tube agglutination of boiled broth cultures with specific "O" sera.

Infections in Children's Hospitals

As has been mentioned previously, the epidemic caused by *S. bovis-morbificans* was declining, and, as infections with other types were not numerous, it is difficult to draw deductions concerning the epidemiology of Salmonella infections. The only fact which emerged clearly was the different infectivity of the various pathogenic organisms under conditions prevailing in a children's hospital. In Table I our experience in this respect is summarized for the twelve months from August, 1949, to July, 1950.

Table I

Patients with Infections Admitted to Children's Hospitals and Hospital Infections

Organism	Patients with Infections when Admitted	Infections Acquired in Hospital	Ratio
S. typhi-murium ..	34	8	4·2 : 1
S. bovis-morbificans ..	10	11	0·9 : 1
S., other types.. ..	14	5	2·6 : 1
Sh. flexneri	22	12	1·8 : 1
Sh. sonnei	164	38	4·3 : 1

The figures in the last column of this table should not be construed to represent the frequency of transmission of organisms from the patients admitted with infections to uninfected patients in the same hospital. The data are presented in this form solely to draw attention to the fact that, although infection with *S. bovis-morbificans* seemed to be rare in the population, hospital infections were much more frequently encountered with this organism than with other types of Salmonella.

A similar discrepancy between the number of infections acquired in hospital and those which originated outside its walls could be demonstrated in the two types of dysentery which were prevalent at the time. Although the number of children admitted to hospital with *Sh. sonnei* infections was seven times greater than the corresponding number of admissions for dysentery caused by *Sh. flexneri*, the relative incidence of hospital infections with the latter organism was very much higher.

These results, which appear almost paradoxical when first considered, can be explained at least partially when the ratio between admissions and hospital cases is followed for a considerable time. Such a constant notification is presented in Table II

for cases of *Sh. sonnei* infections. It must be kept in mind that *Sh. sonnei* was observed for the first time in November, 1949, and that it had not occurred in Brisbane for a considerable period prior to this date, whereas infections with *Sh. flexneri* had been fairly common throughout the previous two years. In Table II, only those cases of hospital infection are considered which appeared to be sporadic, and which were serious enough to cause admission of the child to the gastro-enteritis ward. A severe outbreak of enteritis caused by *Sh. sonnei* in a ward for orthopædic patients has been excluded, and will be discussed later.

TABLE II
Cases of Dysentery Caused by Sh. sonnei in the Hospitals

Year	Month	Admitted to Hospital with Dysentery	Acquired Dysentery in Hospital	Ratio
1949	November	9	1	9·0 : 1
	December	13	2	6·5 : 1
1950	January to March ..	97	33	2·9 : 1
	April to June ..	28	8	3·5 : 1
	July to September ..	14	13	1·0 : 1
	October to December	6	3	2·0 : 1
1951	January to March ..	11	19	0·6 : 1
	April to June ..	11	18	0·6 : 1
	July to September ..	11	17	0·6 : 1
	October to December	12	14	0·9 : 1

It appears that the ratio of patients admitted with infections to hospital infections is high at the beginning of the epidemic, and declines as soon as the infection is well established. During the epidemic under study, it took from November, 1949, to the first quarter of 1951 for the proportion to approach that observed for *S. bovis-morbificans*. This figure was maintained, with minor fluctuations, although the numbers of admissions for infections is considerably smaller than in 1950.

If only these figures are considered, it is not easy to give a valid explanation for the change of ratio. It seems to be fairly certain, however, that the number of patients with clinical infections who are admitted to an isolation ward does not give an accurate indication of the risk of infection within the hospital. In other words, diseases which seem to be highly contagious in the extramural population are not very apt to produce hospital infections during the first few months of their prevalence, and their apparent contagiousness within the hospital increases gradually over a period until a certain ratio is established. In our example the two organisms concerned, *S. bovis-morbificans* and *Sh. sonnei*, finally reached approximately the same figure.

During May, 1951, an outbreak of *Sh. sonnei* infection in an orthopædic ward could be followed. Of the 29 children at risk, 20 had diarrhœa, vomiting or both, and nine remained well throughout. Of the 20 sick children, 17 passed *Sh. sonnei* in the stool, and so did two out of the nine healthy ones. When the first clinical symptoms in the positive cases only are considered, the epidemic developed as follows: May 12, five cases; May 13, nil; May 14, five cases; May 15, four cases; May 16, three cases.

Restricted examination of the staff was performed on May 15 and 16, and the infection could be traced with great probability to a physiotherapist, who had suffered from diarrhœa between May 8 and 13. *Sh. sonnei* was grown from her fæces on May 15 and on one later occasion.

The deduction from our experiences in the hospital can be summarized as follows. There is no constant ratio between the number of children who are admitted to hospital with infections caused by *Sh. sonnei* and the number of sporadic infections which originate within the hospital. A more or less constant proportion would be expected if overt cases among the patients were the main source of infection in a direct or indirect fashion. Whether the number of subclinical infections in hospital patients who are admitted for diseases other than enteritis parallels the number of clinical cases, or rises only after the infection is firmly established in the community, would have to be examined separately. In our material we did not find indications that a "carrier epidemic" preceded the outbreak of the clinical infection, and silent infections with *Sh. sonnei*, although not uncommon, were not of frequent occurrence.

INFECTIONS IN CHILDREN'S HOMES

Exact epidemiological observation is difficult in a hospital, with its quick turnover of patients and large and often-changing staff. During the last three years, regular examinations were performed in five children's homes in the hope of finding an explanation of certain points which could not be studied in the hospitals.

Two of the homes visited admitted only infants on a temporary basis, sometimes with their mothers, mainly for the management of feeding difficulties. Three other homes admitted children of all ages, but examinations in the latter were restricted to children aged under two years, who were cared for in separate buildings.

During the period under study, three major outbreaks occurred in these homes, and the epidemiological observations which were made before and during these outbreaks will be discussed in the following paragraphs.

Outbreak of Gastro-enteritis Caused by E. coli O III

The institution in which this outbreak occurred was housed in what used to be an old-fashioned, large private home. Although alterations had been made, it remained a rambling place with dark corners and passages. Despite these disadvantages, the home was kept spotlessly clean by the unceasing attention of a devoted permanent staff, who supervised and directed large numbers of trainees. Because of the large number of trainees, the home was somewhat overcrowded. Kitchen and distribution of food were beyond reproach.

The introduction of infection was facilitated by the fact that all trainees lived with their families, and came to the home only when on duty. The "resident mothers" and their visitors formed another avenue by which infections could enter. Infants who were admitted alone, and children whose mothers were residents, were taken into the home without previous bacteriological examination. Half-hearted isolation was practised, insofar as most children were admitted to a separate small room, or their cots placed at the end of a row until one bacteriological examination had been performed. As the home was visited only once a week, several days elapsed in many cases before the result of the examination was known.

Normal Period. — Regular observations, restricted to examinations for Salmonella and Shigella, date from August, 1950. Examinations of Escherichia strains from children admitted to this home were first performed on April 9, 1951, and from then onwards more or less regular examinations of this type were performed every few weeks in addition to the weekly examinations for Shigella and Salmonella. The results are summarized in Table III. Study of this table reveals that pathogenic organisms of various groups were introduced on a number of occasions, but no spread occurred. As far as the Escherichia strains are concerned, nothing indicated that a free exchange of groups occurred. Certain groups were encountered more often than others, but no "institutional strain" appeared to become established. It can therefore be stated that regular examinations for Salmonella and Shigella and spot-checks for Escherichia groups failed to reveal an instance which would implicate a child as the starting point of an outbreak.

TABLE III

Pathogenic Organisms and Groups of E. coli in Children Admitted to a Children's Home

Date	Number of Children Examined	Pathogenic Organisms	Pathogenic *E. coli* Groups	Other Groups of *E. coli*
April 9 ..	6	1 *S. adelaide*	1 *E. coli* III	1, 4, 5, 17, 18, 19
April 23 ..	5	1 *S. newport*	—	4, 5, 15, 18
May 7 ..	5	—	—	12, 21
May 21 ..	5	1 *S. typhi-murium*	1 *E. coli* III	3, 6, 7
May 28 ..	3	—	—	2, 21
June 13	4	1 *Sh. sonnei*	—	4, 13, 18
July 23 ..	3	—	—	1, 8, 18, 25
July 30 ..	1	—	—	1
August 30	2	—	—	2, 4
October 8	2	—	—	2, 6

Epidemic.—On October 12, 1951, investigation of an outbreak of diarrhœa and vomiting was requested, the course of which will be described in the following paragraphs. At the time of the outbreak, the home cared for 21 children aged from two weeks to ten and a half months, six of whom were breast-fed.

The first two children had vomiting and loose motions on October 9. These were one healthy child, aged eight months, admitted to the home on September 28 because his mother had to undergo hospital treatment, and a child of nine months, who had been in the home for several months as a "feeding problem". The latter child had had loose motions before, especially between July 26 and August 7—that is, two months before it developed diarrhœa again on October 9—but no pathogenic organism could be isolated in several examinations.

Three further children developed diarrhœa and vomiting on October 12, the day of our visit, and these five children were examined. *E. coli* O III was isolated from four, and no pathogenic organisms from the fifth, a boy of seven weeks who had been admitted to the home for feeding management prior to adoption and was discharged from the home in the care of his adoptive parents on the day of the examination. Later checks revealed that his diarrhœa had subsided after one or two days, and pathogenic organisms could not be isolated at later examinations.

Presented in tabular form, the epidemic developed as follows (Table IV):

TABLE IV
Epidemic Caused by E. coli O 111 (Eleven Cases)

Occurrence of Cases	Date	Number	Infant Population at Risk	
			Artificially Fed	Breast Fed
First cases ..	October 9	2	15	6
Further cases ..	October 12	3	10 (1 discharged)	6
Further cases ..	October 13	1	8 (2 discharged)	6 (1 discharged)
Further cases ..	October 14	1	5	5
Further cases ..	October 21	2	3 (1 discharged)	0
Further cases ..	October 24	1	1	5 (5 discharged)
Further cases ..	October 25	1	0	0

Further bacteriological examinations of the children were performed as follows: on October 19 on 17 children, on October 22 on seven children, on October 29 on 12 children; and final check-ups on October 31 on six children, on November 5 on nine children, and on November 15 on five children.

The results were that *E. coli* O 111 was isolated on one or several occasions from all eleven children who were on artificial diet and remained in the home, but from none of the children who were breast-fed. It is interesting that in several cases *E. coli* O 111 was isolated three to five days before the first clinical signs of infection appeared. Of the artificially fed children, two died, after illnesses of ten and twenty-one days respectively. Of the nine children who survived, five were still passing *E. coli* O 111 on November 5, but all gave negative results at later examinations.

In summary, it may be said that an outbreak of gastro-enteritis affecting every child in the home except six breast-fed children developed between October 9 and 25, 1951, causing the death of two children aged eight months and nine months respectively. At first suspicion was, of course, focused on the preparation of food; but it seems very unlikely that the source of infection was in the formula-kitchen, as preparation and distribution of food were on a very high level of hygiene. Apart from this fact, the onset of the infection was spread out over a period of sixteen days, and the formulas for the different children were prepared individually by different nursing trainees under the general supervision of the permanent staff.

Examination of Adults.—At the time of the outbreak there were 45 adults in the home. These were eight members of the permanent staff, five resident mothers and 32 nursing trainees. All were examined bacteriologically between October 19 and 24, 1951. *E. coli* O 111 was isolated from two trainees; all other examinations, including later examination of the two carriers, gave negative results. Inquiries elicited the fact that one of the carrier nurses was ill with diarrhœa and nausea on October 3 and 4, five or six days before the first clinical case developed in the home. The other had loose motions and a slight upset on October 29, six days after *E. coli* O 111 had been isolated from her fæces. Neither of the two nurses had been employed in the formula kitchen during the critical time, and as no accurate roster was kept in the home, it was impossible to ascertain which children were attended by the individual nurses.

The evidence is only circumstantial that one or both of the nurses were responsible for the spread of the infection, but we think that the history is highly suggestive. None of the children who were admitted to the home at the critical time carried the organism, and the illness of one of the adult carriers occurred at a time which would make her an excellent source of infection. It is also possible, of course, that the other carrier, who was well prior to and during the first part of the epidemic, might have carried the organism at that time.

The resistance of the breast-fed children is remarkable. Apart from being breast-fed and "mothered" by their mothers, these children were cared for by the staff and were in no way separated from the other children. The resistance to infection has to be considered as inherent in breast-feeding, and could not be caused by lack of exposure.

Epidemic Caused by Three Organisms

An epidemic caused by three organisms occurred in a big institution, which cared for children of all ages. The home was housed in spacious, well-constructed buildings, one of which was assigned to the care of children aged up to two years, but shortage of staff made it impossible to apply rigid hygienic rules.

Isolation of children with suspected or known contagious diarrhœa was achieved by confining the child to his cot under a mosquito net. For defæcation, the older children were placed on a chamber pot next to their beds, and as constant supervision was impossible, the floors were often soiled. Disposal of diapers and bed linen was also often insanitary, the soiled pieces being thrown into open containers, with ample opportunity for contamination of the floor,

walls and furniture. When contagious cases of enteritis occurred, nurses wore gowns when attending the patients, but had to care for healthy and sick children alike. The nursing staff of the babies' home was not supposed to work in the houses for the older children, but this rule had to be broken on numerous occasions.

Weekly examinations of a group of children in the babies' home were performed regularly, and, in addition to these "permanents", all children newly admitted to the house were examined. Children who showed signs of an intestinal upset were examined repeatedly, even if the diarrhœa subsided. Children aged over two years, who were cared for in the other houses of the institution, were examined only when suffering from enteritis.

Full scale examinations, including grouping of Escherichia strains, began on April 9 and were continued until October 8, 1951, when the grouping of *E. coli* was abandoned, and the examinations were restricted to the search for *E. coli* O 55 and O 111 and organisms of the Shigella and Salmonella groups.

Because of the complexity of the examinations which were necessary to complete this study, the findings will be shown in three tables representing different periods.

Normal Period.—Table V, representing the time between April 9 and September 10, contains observations which have to be considered as normal in a home of this size in a place where the population is well "seeded" with pathogenic enteric organisms. Pathogenic organisms were sometimes introduced by newly admitted children; at other times they appeared suddenly in children who had been in the home for a considerable time, and no indication could be obtained of their way of introduction. This applies in an identical fashion to organisms of the Shigella group and for *E. coli* O 111. *Sh. flexneri* was introduced into the home only once by a newly admitted child, and, after the initial spread to one other child, the infection stopped. Infections with Salmonella did not occur.

Common to *Sh. sonnei* and *E. coli* O 111 infections was the fact that new infections did not always cause overt disease. Actually, *E. coli* O 111 was found on 15 occasions in children who had to be considered healthy, or whose illness could be ascribed to an infection with *Sh. sonnei*, and in only two instances did its appearance coincide with the onset of diarrhœa. *Sh. sonnei* seemed to produce clinical symptoms rather more often, but silent infections with this organism were not uncommon.

Pre-epidemic Period.—The pre-epidemic period encompasses the period from September 10 to November 26, in which two warnings of an impending outbreak could be noted. The first indication that enteric organisms were able to spread to a number of children within a short time was the sudden appearance and quick spread of *E. coli* group 7. In the fortnight between September 17 and October 1, this organism spread to ten children of the 20 to 25 who were residents at this time. With the exception of the isolated occurrence of *E. coli* O 111 in child number 9 on September 17, the house was free of pathogenic organisms, the only two cases of *Sh. sonnei* infection occurring in older children.

This "silent epidemic" caused by *E. coli* O 7 raises several interesting questions. The first would be obviously the question of origin. *E. coli* O 7 is one of the rare types in Brisbane, and had previously been found only three times during our studies—on April 23, May 21 and May 28 1951—in children of this home. It is unlikely that it persisted for four months in the home without being isolated again at many hundreds of examinations. None of the children who had been admitted to the home in the meantime were carriers of this strain, and we are driven to the conclusion that the strain did not come originally from one of the children, who were all aged under two years and therefore not able to make contacts freely. A further interesting point is the question whether this should be considered as a "pathogenic" organism. Its infectivity is certainly of a high order, greater than that of *E. coli* O 111 and the Shigella organisms which had been introduced into the home in the previous months. None of these organisms were able to infect half the children in the home. If we assume that the source of infection with *E. coli* O 7 was one of the nurses, the infection of a large number of children within a short time would be easy to understand, and it would not be necessary to assume high infectivity associated with low virulence—a combination of attributes which is rare to say the least.

A more ominous sign that the hygienic measures in the home were insufficient to ward off enteric infections was the isolation of *S. typhi-murium* from child number 11 on October 8. Within the next two weeks this organism spread to two more children without giving rise to serious clinical signs. Whether children in a home of this type should be

TABLE V

Bacteriological Examinations in an Infants' Home: Normal Period[1]

Date 1951	Children Examined Regularly: Child's Number[2]													Other Children in Same House	Older Children
	1	2	3	4	5	6	7	8	9	10	11	12	13		
April 9 ..	2, 3 —	21 —	3 —											3: 1 So.	1: 1 So.
April 16 ..	non —	non —	2 —							non —				2: —	2: 2 So.
April 23 ..	7 —	7 —	non —					III						5: —	5: 1 So.
May 1 ..	non —	non —						non —		non —				3: 3, 13, 14, 18, 25	
May 7 ..	21 III	III								non —				5: —	
May 14 ..										non				5: 2, 7, 2, 13, 18	
May 21 ..	7 —	21 III								3 III				1: —	
May 28 ..	non —	non —		6 —	21 —	7, 21 —				III					
June 4 ..	non [—]			non —	non —	—		non [—]		III	—				
June 12 ..	non —	non —		non —	non —	—				non —				1: 2, 21	
June 18 ..	1, 3 —	8, 16 —		6 So.	1 —	non —		non —		3 —		non —	—	1: —	
June 25 ..	non —	non —		non So.	non —					non			non —	4: 4, 6, 8, 18, 21	
July 2 ..	1 —			6, 10 —	non —			[III]		21 —	21 —			5: —	
July 5 ..	10 —			6, 10 —	non —	non —		10 [III]		21 —	non —			3: 1, 4, 18	
July 9 ..	2, 10 —			1, 6 [So.]	12, 21 [So.]	non —		10 III	6 —	21 —	18 —			4: 1, 4, 12, 21	
July 16 ..	10 —			6 —	non [So.]	—		4, 18 —		—	18, 23 —			5: 1, 3, 6, 12	6: —
July 23 ..	non —			6, 10 —	non —	21 —	non [Fl.]	4 —		non —	—	4, 18 III	12, 21 —	3: 6, 12, 21	
July 30 ..	10 —			6 —	non —	21 —	non [Fl.]	4, 18 [Fl.]		—	—	4 —		2: 18, 21 III	
August 6 ..	non —			1 —	non —	21 —	15 —	non —	[III]	—	21 —			3: 4	
August 13 ..	4 —			III	III	—	15 —	non —	[So.], III	III	4 —		non [—]	3: 2, 21 III	
August 20 ..	18 —			1, 6 —	10 III	non —	18 —	21 —	6 [So.], III	10 —	4, 18 —				4: 4 So.
August 27 ..	18 —			6 —	non —	—	non —	non —	2, 6 —	non —	25 —	21 —	non [—]		3: 6 1 So., III
September 3	10 —			4, 6 —	non —	non —	non —	9, 21 —	2, 6 —	non —	—	4, 18 —	4, 18 —		4: 1 So.
September 10	non —			non —	—	—	non —	9, 21 —	6 —	—	—	—	—		3: 1 So.

[1] Explanation of symbols: "non", non-groupable strains of *E. coli*; numbers such as 1, 4, 6, III, indicate *E. coli* groups; "Fl.", *Sh. flexneri*; "So.", *Sh. sonnei*; [ ], child sick with diarrhœa and/or vomiting; " — ", no pathogenic organisms found.

[2] The top line for each date gives the groups of *E. coli* which are not known to be pathogenic; the bottom line is reserved for known pathogens.

TABLE VI

Bacteriological Examinations in an Infants' Home: Preepidemic Period[1]

Date 1951	Children Examined Regularly: Child's Number[2]															Other Children in Same House	Older Children
	1	4	5	6	8	9	10	11	12	13	15	16	17	18	19		
September 10..	non —	non —	—	—	9, 21 —	6 —	—	—	—	—	—					2: non —	6: 2 So.
September 17..	non —	—	7 —	—	—	III	7 —	non —	—						4, 18, 21 —	2: non —	5: 2 So.
September 24..	7 —		— —	7 —	4, 18 —	7 —		7 —	7 —	—					7, 18 [—]	2: non —	6: —
October 1 ..	21 —						— —	4, 18 —	non —	non —			7 —		non —		3: 3 So.
October 8 ..	7 —				2 —	— —	2, 4 —	4 Sal.		7 —	—	—					4: —
October 15 ..	[Sal.]						— —	— —		— —						1: —	5: 3 So.
October 18 ..	—						— —	— —									5: 1 So.
October 22 ..	[Sal.]						— —	— —		Sal. —							3: —
October 25 ..								— —		— —		6 —					2: —
October 29 ..	Sal. —						— —			— —		non —					1: —
November 5	non Sal.						non —					non —		— —			2: —
November 8	non —									non —		III —					
November 12	— —						non —		non [—]	— —							
November 19	—						Sal. —		[—]							1: —	
November 20	—						— —		[—]					[—]			

[1] Explanation of symbols: "non", non-groupable strains of *E. coli*; numbers such as 1, 4, 6, III, indicate *E. coli* groups; "So.", *Sh. sonnei*; "[ ]", child sick with diarrhœa and/or vomiting; "—", no pathogenic organisms found; "Sal.", *S. typhi-murium*.

[2] The top line for each date gives the groups of *E. coli* which are not known to be pathogenic; the bottom line is reserved for known pathogens.

considered as healthy or ill when they produce a few loose stools or suffer a slight loss of weight is a highly debatable question. None of the Salmonella carriers was seriously ill at the time, and the isolation of the organism came as a surprise to the sister in charge of the home. Again the question of origin remains unsolved, and this enforces a conclusion which has been indicated in earlier paragraphs.

The introduction of pathogenic organisms into a children's home cannot be recognized and prevented by regular and painstakingly performed examinations of all newly admitted children. Actually, the discovery that pathogenic organisms were present in the home was made on several occasions by the examination of children who had been in the home for many months and did not show any signs of intestinal infection. Only once, in the child infected with *Sh. flexneri*, was infection recognized in a newly admitted child.

Epidemic.—The actual outbreak of gastroenteritis was in no way remarkable, apart from the fact that three organisms were involved. The onset was sudden, eight children sickening on December 1, 1951. The findings are presented in Table VII.

The examination on February 11, 1952, extended to all children in the home, who were all doing well at the time and remained healthy, although pathogenic organisms continued to appear in a haphazard fashion during the following weeks. On February 18, *Sh. sonnei* was isolated in three cases and *S. typhi-murium* in one; on February 25, in three cases *Sh. sonnei* was isolated, on March 3 in one case, and so on. None of the organisms could be traced to a newly admitted child, and there

seemed to be no connexion between the consecutive cases of the different infections. The sporadic cases of Salmonella infections in the midst of an institutional outbreak caused by Shigella and Escherichia strains were particularly impressive.

TABLE VII

Bacteriological Examinations in Infants' Home—Epidemic Period

Date of Examination	Number of Subjects Examined	Organisms Recovered
1951—		
December 3	10	*E. coli* O 111, five cases; *Sh. sonnei*, one case.
December 10	15	*E. coli* O 111, four cases; *Sh. sonnei*, six cases.
December 17	23	*E. coli* O 111, four cases; *Sh. sonnei*, 10 cases; Salmonella, one case.
December 27	12	*E. coli* O 111, two cases; *Sh. sonnei*, two cases; Salmonella, one case.
1952—		
January 2..	19	*E. coli* O 111, two cases; *Sh. sonnei*, eight cases; Salmonella, one case.
January 7..	11	*Sh. sonnei*, five cases.
January 14..	10	*E. coli* O 111, five cases; *Sh. sonnei*, one case; Salmonella, one case.
January 21..	15	*Sh. sonnei*, five cases; Salmonella, one case.
January 29..	11	*E. coli* O 111, one case; *Sh. sonnei*, three cases.
February 4	13	*Sh. sonnei*, one case; Salmonella, one case.
February 11	26	*Sh. sonnei*, four cases.

Only circumstantial evidence concerning the origin of the outbreak could be obtained. Two nurses volunteered the information that they had suffered from diarrhœa in the week from November 26 to December 3, 1951, but could not remember the exact date. A single bacteriological examination on December 12 gave negative results, and none of the other nurses could be examined. The epidemiological history is significant, but evidence remains inconclusive.

Infections in Adults

In the previous paragraphs, evidence was presented that even the most rigid bacteriological examination of the children who are admitted to an institution is no safeguard against the introduction of pathogenic enteric organisms. By implication, this indicated the staff as the original source in the majority of intestinal infections in homes of this kind.

By the cooperation of everybody concerned, we had the opportunity to make simultaneous examinations of children, resident mothers and staff in a home which admitted only infants for the overcoming of feeding difficulties. All newly admitted children were examined by rectal swabbing immediately after their admission to hospital. Resident mothers were asked to submit a specimen of fæces on the morning after their admission, and similar specimens were collected at short intervals from members of the staff. The results are presented in Table VIII.

The results confirmed the opinion which we had formed after our previous experience. Infections with pathogenic enteric organisms amongst the staff and mothers were more frequent than in their charges, so that the adults

TABLE VIII

Examination of Children and Adults in an Infants' Home

Series	New Babies	Resident Babies	Mothers	Staff	Remarks
January, 1952:					
Examined	20	0	0	13	New trainee: *S. london*; well.
Positive findings ..	0	0	0	1	
February, 1952:					
Examined	21	0	0	4	
Positive findings ..	0	0	0	0	
March, 1952:					
Examined	20	10	9	28	Mother: *E. coli* O 55; distressing diarrhœa and vomiting two months earlier.
Positive findings ..	0	0	1	1	Trainee: *Sh. sonnei*; off duty for one week, diarrhœa and nausea.
April, 1952:					
Examined	24	6	15	66	Mothers: One *E. coli* O 55; well (different person from the one examined in March); one *S. bovis-morbificans*.
Positive findings ..	0	0	2	4	Staff: One *E. coli* O 55 (sister; well); one *Sh. sonnei* (trainee; mild diarrhœa for three days); one Salmonella (trainee; diarrhœa and nausea for three days—her mother also affected); one *E. coli* O 55 (sister; well).
Totals:					
Examined ..	85	16	24	111	
Positive findings	0	0	3	6	

in a children's home have a correspondingly greater opportunity to become spreaders of enteric organisms than the children. This seems obvious when the problem is considered dispassionately, as adults make a much greater number of contacts and lead a much less sheltered existence than do infants or even pre-school children.

More interesting are two other points which will require close study before it will be possible to form a definite opinion.

If the infection rate which we found in this examination is general, every person in Brisbane who is of school age or older should acquire several infections with pathogenic enteric organisms per year, and should develop a basal immunity within a short time. Actually, the mothers, nurses and nursing trainees whom we examined in this series had probably cleaner habits and were better aware of the dangers of infection than the general population, and their infection rate while living or working in the home should therefore be lower than average. It is significant that four of the adults who were found to be infected gave a definite history of recent enteritis. Of these histories, three were very clear, and indicated without much room for doubt that the infection found had caused the upset, the only doubtful history being given by one of the resident mothers, who was found to be infected with *E. coli* O 55. She gave a history of having had distressing diarrhœa and vomiting two months earlier, during her eighth month of pregnancy, which induced her to visit her doctor several times and to take a variety of drugs prescribed by him, the local chemist and several friends. She stated definitely that only a full course of sulphadiazine was able to stop her enteritis, and that previous dieting, home remedies and patent medicines were of no avail. Her child, who was seven weeks old when first examined, had never had enteritis, and, apart from being a "lazy feeder", was perfectly well. *E. coli* O 55 could not be isolated from his fæces, despite several very thorough examinations.

It is interesting that the proportion of "silent" infections in adults does not seem to be much higher than in infants and young children, and particularly important seems to us the fact that the first three carriers of *E. coli* O 55 who were found in Brisbane were adults and not children.

Outbreak of Enteritis Caused by Shigella Sonnei

The institution in which an epidemic of *Sh. sonnei* enteritis occurred was a semi-private children's home, which was used as a training school. Buildings and grounds were excellent and kept very clean, although both the old building, which housed children aged from seven months to six years, and a so-called new building, which was reserved for babies, were not very suitable as a children's home. The staff consisted of five nursing sisters and an honorary physician, who was responsible for the general medical arrangements in the home. The children who were taken into the home, however, were looked after by the respective family doctors. As the home was visited only after the outbreak, information of happenings before and during the outbreak is second hand.

At the critical time, the following persons were either housed or employed in the home: 21 children in the new building (aged from birth to seven months); 35 children in the old building (aged from seven months to seven years); 5 members of the nursing staff; 18 trainees; 3 members of the domestic staff; 18 resident mothers.

The first case of diarrhœa and vomiting to attract the attention of the nursing staff was in one of the resident mothers, who became ill on April 24, 1952. Three more of the resident mothers fell ill on May 5 and 6. Two of the older children living in the old building fell ill on April 24 and May 2. Four more had to be sent to hospital at various dates, the last being admitted to hospital on May 17. The first baby to be sent to hospital showed signs of enteritis on May 8, and two more sickened on May 12.

Study of the outbreak was requested by the Department of Health and Home Affairs, and the first bacteriological examinations were made on May 27. *Sh. sonnei* was isolated from the stool of two trainees; all other persons in the home were found to be free of *Sh. sonnei* infection.

One of the infected nurses had been working from April 21 to May 5 in the kitchen in which the food for the adults and older children was prepared. The other nurse was working in the nursery for the older children at the same time. On May 5 both were transferred to the new building in which the babies were housed, one working in the nursery, the other in the milk kitchen. During these periods both suffered from diarrhœa and occasional vomiting.

As the first cases among the older children and resident mothers occurred on April 24, and among the babies on May 9 and 12, very little doubt remains that the outbreak was caused by the two infected nurses.

Occurrence of E. coli O 55.—Incidental to these examinations, but more interesting than the obvious epidemiological features of the outbreak of *Sh. sonnei* dysentery, was the discovery of the first two carriers of *E. coli* O 55 amongst children. In the previous section, the finding of three adult carriers of this organism in another children's home has been reported. The two children were taken into the home for non-medical reasons and, according to reports from the nurses and family doctors, were perfectly well. The younger of the two, a boy aged two years, had been in the home for many months; the older, a boy, aged six years, had entered the home a few weeks previously and left before the examinations were completed.

One week after these two carriers had been discovered, the same organism was found in the fæces of a girl, aged fourteen weeks, who had slight diarrhœa, passing three to five liquid, greenish stools per day. As the two older children were living in the "old building", and the baby was in the nursery which was located in the "new building", the transfer could not possibly have been by direct contact; it either must have occurred through an intermediary, or all three infections have had a common source.

So far, no indications have been found which would definitely point to one of the two alternatives, but general epidemiological considerations strongly favour a common source of infection, not only for the three cases which are under discussion, but also for the three adult carriers who have been described previously.

As has already been mentioned, examinations for the various groups of *E. coli* date from April, 1951, and were therefore performed for almost a full year before the first adult carrier of *E. coli* O 55 was located in March, 1952. In April, 1952, two more adult carriers were discovered among the staff of the same home. In June, during the first visit to the home now being considered, two children were found to be infected. The two homes were located in the same suburb of Brisbane within a few hundred yards of each other, but there was no official connexion between the two. The administration was carried out by two different groups, and there was no interchange of staff or patients.

All these facts make it very likely that a common source, located probably outside the institutions but in contact with both, had caused both groups of infections. Otherwise one would have to assume a coincidence, which, although possible, seems to us highly improbable.

DISCUSSION

The experience which has been accumulating over the last three years seems to indicate that, under the conditions prevailing at present, adults are the dangerous spreaders of infections in institutions which care for young children. Obviously there will be occasions in which an outbreak is caused by a child, who either is ill or carries an infective organism without clinical symptoms. It will depend mainly on the hygienic conditions in the institution which of the many pathways of infection will lead to an epidemic more often than others.

The higher the level of hygiene, the more restricted will be the ways by which enteric organisms will be able to infect a number of children within a short time. Most difficult to block will be the transfer of pathogenic organisms from nurse to child, and the high level of hygiene in the homes was probably the determining factor for the epidemiology of the outbreaks described in this paper.

In this connexion, it should be stated that a number of insanitary practices have been abandoned since Mackerras and Mackerras made their studies of the epidemiology of Salmonella infections. It must be considered, further, that in the outbreaks which we were able to observe, no conclusive proof could be obtained that an adult was actually the spreader, although we are satisfied that our findings leave very little room for doubt. Proof will be impossible to obtain, until bacteriological examinations of fæces of nurses, doctors and domestic staff are carried out at short intervals, and particularly whenever a nurse has the slightest intestinal upset.

Although a great number of infections are probably entirely asymptomatic, it has still to be studied whether subclinical infections are as dangerous as overt cases. In all outbreaks which occurred during the last three years, clinically recognizable cases occurred amongst staff members, and the epidemiological study indicated these as likely sources of infection. We think that, if these nurses had reported their illnesses and been put off duty, all these outbreaks might have been prevented.

A problem of major importance seems to be why infected nurses do not spread their infection more often. According to our findings, hardly a week should pass without one of the adults in the homes harbouring pathogenic enteric organisms. Despite this, outbreaks or even sporadic infections are not very common in well conducted institutions.

Clearly it is impossible to form hard and fast rules for the prevention of enteric infections in

children's homes. Infections of adults, and even of children, are much more frequent than would appear from purely clinical examinations. Only regular and frequent bacteriological examinations, not only of newly admitted subjects, but of staff and old inmates as well, would indicate the frequency of infective persons in a given community. Regular grouping of Escherichia strains would be a valuable check on standards of hygiene. We think that such examinations are essential for planning preventive measures, and should be considered as a regular routine by all concerned. With the technique which has been in use for the last few years, we have been able to account for every institutional outbreak which has come to our notice. Refinements are desirable, and will be introduced as soon as practicable, but even present methods applied judiciously should give useful warnings to those responsible for the management of children's homes in the great majority of instances.

It is also clear that only a part of the bowel infections will be discovered even by the most frequent examinations, and that apparent freedom from infection cannot be made an excuse for breaches in hygiene. In general, it can be assumed that very elaborate precautions will not be necessary in institutions which care for normal children past the first few weeks of life, and ordinary domestic cleanliness *plus* regular examinations should be sufficient to prevent the great majority of outbreaks. We think that more attention should be paid to digestive upsets, however slight, whether they occur in patients or among the staff. A little care in this respect would probably do more for the prevention of outbreaks than elaborate mechanical precautions, such as the institution of cubicled wards and the wearing of gloves and gowns by the staff, especially as these last-mentioned precautions tend to become mechanical and ritualistic after a short time.

SUMMARY

The epidemiology of two outbreaks caused by *Sh. sonnei*, one epidemic caused by *E. coli* O 111, and one caused by three pathogenic organisms, has been studied. A small series of infections with *E. coli* O 55 is also described.

In none of these outbreaks could children be implicated as spreaders of the infection. Aerogenous spread and transfer through food were also considered unlikely.

In all outbreaks, adult carriers or mild intestinal infections in adults were implicated, and would suffice to explain the introduction of infection into the homes and primary spread among the children.

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CYANOTIC HEART DISEASE WITH CONTINUOUS MURMUR[1]

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Of the 41 cyanosed patients explored since the inception of the Cardio-surgical Clinic, three had continuous murmurs simulating that of patent *ductus arteriosus*. These murmurs were all found to be associated with cyanotic heart disease, there being no cases of arterio-venous aneurysm of the lung. Perplexing at first, these murmurs have been a recurring source of interest. Helen Taussig (1947), in her chapter on *truncus arteriosus*, briefly recorded a case in which there were two large collateral vessels and a continuous murmur. Though she described it as a case of *truncus arteriosus*, her diagram illustrating the pathology showed an atretic pulmonary artery arising from the right ventricle. Paul Wood (1950) mentioned three cases of continuous murmur in which necropsy revealed pulmonary atresia (Fallot type), the murmur depending on a broncho-pulmonary anastomosis at a fairly high arterial level. Allanby *et alii* (1950), in a study of six cases of pulmonary atresia at Guy's Hospital, recorded two in which continuous murmurs were present. In one of these the murmur was due to a patent *ductus arteriosus*; in the other it was due, at least mainly, to a large anomalous artery which arose from the anterior aortic sinus close to the right coronary artery and entered the pulmonary artery just above the valve.

The following study was undertaken to see whether anything further could be learnt as to the cause and clinical significance of the murmur.

Case Histories

Case I

The first patient, Frances N., aged six years, was examined in October, 1948. She had been slightly cyanosed since the age of two years and had squatted since the age of four. She had borderline polycythæmia and her activities were considerably restricted by fatigue and dyspnœa. In the second left intercostal space there was a grade 3 continuous murmur loudest in late systole, and the second sound was accentuated. It was distinguished from a to-and-fro murmur by its continuity and homogeneous character, there being no interruption between systole and diastole and no detectable difference of pitch or quality between its systolic and diastolic components. Although loudest in the second left intercostal space, the whole murmur was well conducted to the left axilla and left scapular region; it was also clearly audible in the second right intercostal space and faintly audible in the right axilla. The murmur was indistinguishable from that of patent *ductus arteriosus*. There was no thrill. The X-ray film, as reported by Dr. N. Klein, showed an enlarged right aortic arch and right descending aorta. The main branches of the aorta came off in the reverse of the normal order, the innominate being on the left. The pulmonary artery segment was straight and hilar markings were increased. The electrocardiogram showed incomplete right bundle branch block indicating right ventricular enlargement.

On the basis of the cyanosis, the electrocardiogram and the X-ray appearances of heart and aorta we made a diagnosis of Fallot's tetralogy, and to account for the continuous murmur and increased hilar markings, we postulated a patent *ductus arteriosus*.

A year later an angiocardiogram strongly suggested *truncus arteriosus*, but we hesitated to accept this diagnosis as we had not seen a child with truncus who squatted. To clinch the diagnosis, therefore, and in the hope of being able to improve the pulmonary circulation, Mr. Douglas Robb explored the chest on its left anterior aspect. This exposure demonstrated a large overriding aorta and a very small pulmonary artery measuring at its narrowest part only one-eighth of an inch in external diameter. The case was thus one of Fallot's tetralogy, in which the proximal part of the pulmonary artery was atretic. There was no ductus, but under the parietal pleura just posterior to the hilum there was a knuckle of artery about a quarter of an inch in diameter which transmitted a medium thrill. This vessel was thought to come across from the descending aorta behind the viscera of the mediastinum. From the anterior approach Mr. Robb could not actually follow it into the lung, but he had no doubt that it anastomosed with the left pulmonary artery, and that this anastomosis was the seat of the murmur and thrill. A marked but not gross development of collateral thin-walled blood vessels was also noted. As the left pulmonary artery was considered to be too short and small for a Blalock-Taussig anastomosis, only a pleurectomy was performed.

Case II

James N., aged seven years, presented with a similar combination of cyanosis and continuous murmur. This murmur was also of grade 3 intensity with late systolic accentuation, loudest in the first and second left intercostal spaces, well conducted over the whole of the left side of the chest and up the carotid arteries, and also audible, though less clearly, over the whole right side of the chest. Both heart sounds were unusually loud and clear. There was a systolic lift

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FIGURE I

A vinylite cast showing the bronchial tree and the blood supply to the left lung (Case II). Green vinylite was injected into the left pulmonary artery. The dark vinylite which was subsequently injected into the aorta (*a*) has filled the bronchial artery (*b*), and passing through the anastomosis (*c*) has displaced the green vinylite from the primary branches of the pulmonary artery (*p1*) and from some of its secondary branches (*p2*)

widely distributed over the whole precordium from the left to the right mid-clavicular line. The electrocardiogram showed right ventricular hypertrophy and P pulmonale. Catheterization failed owing to abnormality of the subclavian veins on both sides. An X-ray examination, reported on by Dr. A. F. Crick, revealed a large right aortic arch, a pronounced pulmonary bay, a large artery in the left hilum and normal vascularization of the lung fields. Angiocardiography showed dye in the aorta in two and a half seconds and a shadow which was considered to be the left pulmonary artery arising from the aorta. We found ourselves in the same diagnostic quandary as before, and, falling into the same trap, thought we were dealing with a *truncus arteriosus* combined with a small patent ductus. For confirmation and in the hope of finding conditions suitable for a Blalock-Taussig anastomosis, a thoracotomy was performed by Mr. Douglas Robb, the chest being opened this time through a postero-lateral incision. This showed the pulmonary artery to be large and flabby and apparently blind at its proximal end. (Subsequent autopsy showed that it did in fact arise from the right ventricle, but the orifice was obliterated). A coarse thrill was felt posteriorly, where a greatly enlarged bronchial artery, coming off the right-sided aorta and passing behind the œsophagus, entered the left hilum of the lung. There was no *ductus arteriosus*. It was decided to anastomose the left subclavian artery to the left pulmonary artery, which necessitated the clamping of both these vessels. When the anastomosis was under way the circulation began to deteriorate, and just before its completion serious deterioration occurred. Although the clamps were quickly removed and the anastomosis was faultless, irreversible metabolic changes had occurred and the boy died within half an hour.

At autopsy it was found that only a few small anastomotic channels were present in the right hilum, and that almost the whole of the blood for both lungs had been supplied by the large left bronchial artery previously mentioned. Mr. Rowan Nicks injected green vinylite into the pulmonary artery, red vinylite into the aorta and clear vinylite into the bronchial tree. When the tissues were dissolved away a cast was obtained (Figure I), which clarified the arterial anatomy. It demonstrated a single left bronchial artery which, after giving off a small descending branch, anastomosed directly with a primary branch of the left pulmonary artery within the hilum of the lung. From this anastomosis blood flowed not only to the left lung but also via the left and right pulmonary arteries to the right lung. The cause of the disaster was now clear. The greater part of the left lung having been deflated to expose the operative field, respiration had depended upon the right lung, whose main blood supply had been shut off by the clamp on the left pulmonary artery. Death was due to general anoxia, which developed in spite of adequate respiratory ventilation and adequate cardiac output. It was also possible to imagine the large amount of blood that had been driven under relatively high pressure (brachial artery 105 millimetres of mercury, systolic, 65 millimetres, diastolic) through a single bronchial artery into a large pulmonary artery where the pressure was very low. The speed of flow through the orifice, especially at the peak of the pulse wave, undoubtedly accounted for the continuous murmur.

Case III

Joan T., aged sixteen years, was examined in August, 1952. She had been slightly cyanosed since birth and had slight clubbing of the digits and borderline polycythæmia. Exercise tolerance had always been restricted considerably by fatigue and dyspnœa, but had improved slightly during the previous five years, enabling her to walk a few hundred yards on the flat. Her hands and feet were cold, the jugular venous pressure was slightly raised, and there was a slight right ventricular lift. The second heart sound was single and accentuated. There was a grade 3 continuous murmur loudest in the first right intercostal space, well conducted along the carotid arteries and throughout the entire chest, especially on the right side. The X-ray film, as reported on by Dr. J. D. Recordon, showed a typical heart of the "*cœur en sabot*" type with a pronounced concavity in the region of the pulmonary artery, a wide, unfolded and unduly pulsatile aorta and slightly deficient lung fields. The left hilar shadow suggested a number of small vessels, and two abnormal impressions upon the œsophagus suggested dilated bronchial arteries. The electrocardiogram showed incomplete right bundle branch block indicating right ventricular enlargement. Catheterization revealed considerable right ventricular hypertension, the pressures being systolic, 140 millimetres of mercury, diastolic, 0, mean, 58 millimetres of mercury. The catheter failed to enter the pulmonary artery in spite of a good "lie", but for the first time in our experience found the aortic outlet and entered the innominate artery. Oxygen saturation tests failed to demonstrate any left-to-right shunt through either septum. The degree of cyanosis was indicated by the oxygen saturation of 84% in the innominate artery. Bearing Case II in mind, we decided that this must be either Fallot's tetralogy with atretic or very small pulmonary artery, or *truncus arteriosus* with no pulmonary branches, the murmur being due to a single large right bronchial artery anastomosing with the right pulmonary artery.

It was, therefore, decided to explore from the left side, and if conditions were favourable to increase the blood supply to the lungs by a Blalock-Taussig anastomosis. Mr. Rowan Nicks thereupon exposed the left hilum from the postero-lateral aspect and the following were his observations:

> There was very great collateral circulation. The lungs appeared healthy but pale. The pulmonary artery was atretic for about an inch then dilated into a trumpet-shaped vessel from which upper lobar branches arose. It was thin walled, carried virtually no pressure and did not appear to communicate with the right side. Peripherally there was a thrill and a broncho-pulmonary anastomosis was confidently diagnosed. A vessel in the lingular region was distended, tortuous and obviously received blood directly from the bronchial system.

The proximal atretic end of the pulmonary artery was clamped, and as no deterioration in the pulmonary circulation ensued during the next half hour this vessel was ligated and divided. The left subclavian artery was then brought down and anastomosed end to end with the left pulmonary artery, a good flow of blood resulting. Peak blood pressures on completion of the operation were as follows: aorta and left subclavian artery, 120 millimetres of mercury, left pulmonary artery, 30 millimetres of mercury. As was to be expected, the patient derived considerable benefit from the extra anastomosis.

In this case both lungs independently derived their main blood supply from the bronchial system. In addition to a great number of small anastomotic

vessels at least one large bronchial artery anastomosed with each pulmonary artery. The broncho-pulmonary anastomosis on the right side, where the murmur was louder, proved adequate to sustain respiration throughout the operation.

THE CAUSE OF THE MURMUR

Most patients with Fallot's tetralogy and *truncus arteriosus* who survive for more than a few years are found at operation to have some degree of mediastinal collateral anastomosis. Of the 41 cases included in this study, some mention of the collateral circulation was recorded in 34 (Table I). From Mr. Douglas

TABLE I

Number of Vessels	Number of Subjects	Continuous Murmur
Nil	4	Nil
Few	9	1 case
Moderate	12	1 case
Considerable or gross ..	9	1 case
Not recorded	7	Nil

Robb's and Mr. Rowan Nicks's operation notes the numbers of these vessels may be assessed as nil in four cases, few in nine cases, a moderate number in 12 cases and a considerable number in nine cases. In no case was a thrill felt or pulsation observed among the network of small vessels. It will be seen that of the 30 cases in which collateral vessels were noted, their numbers were moderate or considerable in no less than 21. Yet, as has been stated, only three patients had continuous murmurs. It is clear, therefore, that the incidence of the continuous murmur does not depend on a profusion of vessels. It was also noted that among the 41 subjects explored there were seven in which the external diameter of some part of the pulmonary artery was one-third of an inch or less, including five cases in which it was reduced to one-eighth of an inch (Table II). These seven cases include the three which have been described in some detail above and three others in which there was a moderate or a considerable number of collateral vessels. It is clear, therefore, that an atretic or very small pulmonary artery, even when compensated by a moderate or considerable number of anastomotic vessels, does not necessarily cause a continuous murmur. It is surely significant that the murmur was heard and a continuous thrill felt at operation in the only three cases in which the blood was conveyed to the lung mainly by a single large bronchial artery or a very small number of large bronchial arteries which anastomosed directly with a large flabby pulmonary artery. It is also significant that similar large broncho-pulmonary anastomoses were present, as

TABLE II

Subject.	Age (Years)	Size of Pulmonary Artery	Number and Size of Anastomoses	Continuous Murmur
M.B.	16	One - eighth inch.	Not recorded.	–
M.W.	16	One - eighth inch.	Moderate number, small.	–
D.R.	10	One - third inch.	Considerable number, small.	–
K.H.	8 months	Very narrow.	Not recorded.	–
J.N.	7	One - eighth inch	Single large and a few small.	+
F.N.	7	One - eighth inch.	Single large and moderate number of small.	+
J.T.	16	One - eighth inch.	At least two large and considerable number of small.	+

previously noted, in Taussig's and Wood's cases, and that large arterial anastomoses, albeit of different kinds, were present in the two cases reported by the Guy's Hospital team.

CONCLUSIONS

Although our three patients, Paul Wood's three patients and the two patients from Guy's Hospital all had pulmonary atresia, and although Helen Taussig's case would now, we think, be classified as one of pulmonary atresia, it is probably not justifiable to assume that every patient with cyanotic heart disease and a continuous murmur has pulmonary atresia, for in the more primitive type of *truncus arteriosus* in which the developing pulmonary artery fails to join either the ventral or the dorsal aorta, and in which, therefore, the truncus has no pulmonary branches and there is no *ductus arteriosus*, the main blood supply to the lungs must be derived from the bronchial arteries. In some of these cases, as in pulmonary atresia, it is to be expected that there would be one or more large broncho-pulmonary anastomoses from which continuous murmurs would arise. This type of truncus, however, is exceedingly rare, and its distinction from pulmonary atresia is of no clinical importance. For all practical purposes, therefore, when a continuous murmur is found in association with cyanotic heart disease, an atretic pulmonary artery compensated mainly by one or more large arterial anastomoses may be diagnosed confidently. In our three cases and in four of the six cases reviewed from the literature, the anastomoses were

broncho-pulmonary. Though it can seldom be demonstrated, it has seemed reasonable to assume that the murmur and thrill arose at or very near the seat of the anastomosis. That this may not always be so, however, is suggested by the sixth of the Guy's Hospital cases, in which a thrill was felt in a bronchial artery and in which at subsequent necropsy no macroscopically evident anastomosis was present. The cause of the vibration in this artery was not discussed and its audibility at the surface was not clearly indicated. Notwithstanding this most unusual finding, there must be very few exceptions to the rule that the major source of blood supply to the lungs will be found on the side on which the murmur is louder.

The danger of occluding the pulmonary artery on the same side as the main arterial supply was illustrated by our Case II. It is, therefore, recommended that when a Blalock-Taussig operation is undertaken in such a case the chest should be opened on the side on which the murmur is more difficult to hear. Our experience with Case II also emphasizes the wisdom of clamping the pulmonary artery at an early stage of the operation, so as to make sure, before that vessel is opened, that what remains of the pulmonary circulation is sufficient to maintain life.

ACKNOWLEDGEMENTS

I wish to express my gratitude to Mr. Ross Nicholson for help in searching the case records, to Mr. Douglas Robb and Mr. Rowan Nicks for valuable suggestions and for their excellent operation notes which provided much of the data for this study, and also to Mr. R. W. Litherland for the figure.

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THE SPATIAL VECTORELECTROCARDIOGRAM IN THE LEFT VENTRICULAR HYPERTROPHY OF HYPERTENSION[1]

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The spatial vectorelectrocardiograph (VCG) is now being used in many cardio-vascular centres in an attempt to gain more complete understanding of the changes in electrical activity of the heart in disease. The theory of this method and an outline of its technique have been the subject of a recent paper (Lowe and Goble, 1952), with an analysis of the results obtained in 104 normal individuals. Various papers—notably, the writings of Duchosal and Sulzer (1949), of Donzelot, Milovanovich and Kaufmann (1950), and of Grishman and Scherlis (1952)—have presented analyses of the tracings found in various types of heart disease, but as yet the number of patients examined has been small.

In this paper an analysis is presented of the VCGs obtained in a series of 68 cases of established hypertension, and the patterns found are described.

CLINICAL MATERIAL AND METHODS

The series consists of 68 patients with established hypertension attending the Alfred Hospital. For the purposes of this analysis, the criterion of selection was the presence of persistent elevation of the diastolic blood pressure to 110 millimetres of mercury or more. The majority had clinical or radiological evidence of left ventricular hypertrophy; in the remainder there was strong presumptive evidence that this was present to some degree. The patients varied widely in their clinical state. Most were considered to be examples of essential hypertension, but some had hypertension due to chronic renal disease. The great majority had come to hospital for relief of symptoms associated with hypertension, and the series therefore necessarily includes a high proportion of relatively severe cases; 20 patients, in fact, were considered to be in the malignant phase of hypertension. A few were asymptomatic.

The ages of the patients ranged from twenty-five to seventy-six years, with a mean of forty-eight years. Outstanding symptoms related to the cardio-vascular system were as follows: dyspnœa on exertion in 51 cases, paroxysmal nocturnal dyspnœa in 20, *angina pectoris* in nine. Twenty patients had suffered from congestive cardiac failure at some time; none had certainly had a cardiac infarction. In no case was the hypertension thought to be complicated by valvular lesions.

The VCGs were recorded by the methods previously outlined, the electrode placement of Duchosal and Sulzer being used. The vector synthesis was achieved electronically, improved amplifiers and cathode ray oscilloscopes being employed. In later cases two channels were used to record the spatial loop simultaneously in two projections at right angles. The orientation of the projections is indicated in Figure I. As an aid to study, models have been made of several loops thought representative of the patterns found (illustrated in Figures IV, VI and VIII). With practice the observer finds that he can gain a fairly accurate picture of the loop in space on inspection of the three standard projections.

RESULTS

Analysis of the Auricular (P) Complex

All patients had sinus rhythm. The auricular complex (*P* loop) showed no outstanding features. It was small or normal in size, narrow and pointed in some, bifid in others (but not so obviously as in some cases of mitral stenosis), and pointed downwards, either vertically or a little to the left.

Analysis of the Ventricular (QRST) Complex

Duration of the QRS Loop.—In the normal subjects previously analysed, the duration of the *QRS* loop varied from 0·6 to 0·8 second.

[1] Received for publication on December 18, 1952.

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[3] Part of the expenses of this investigation were defrayed by a grant from the National Health and Medical Research Council.

In this group, eight patients had a *QRS* time of 0·10 second or longer. This time was taken to be abnormal, although, as one tracing was normal in all other respects, it is possible that this limit is too short. Two of the eight patients showed the pattern of left bundle branch block.

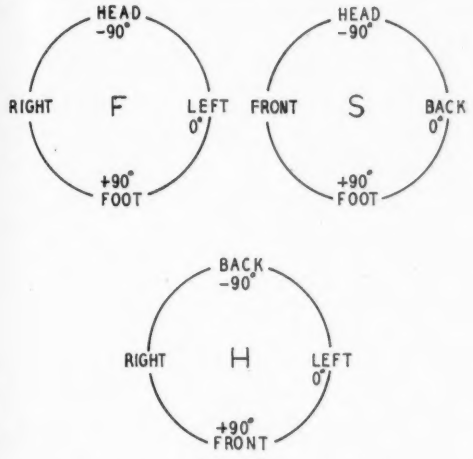

FIGURE I
Diagram to show the orientation of the VCG loops in all illustrations

Direction of Inscription of the QRS Loop.—Normally the frontal loop may be written in either anticlockwise or clockwise direction, or as a figure-of-eight. In this series 45 frontal loops were written anticlockwise, nine clockwise and 14 as a figure-of-eight. Normally the sagittal and horizontal loops are written anticlockwise. In this series, two sagittal loops were written clockwise, and five as a figure-of-eight, while the horizontal loop in three cases was a figure-of-eight (Table I).

TABLE I
Direction of Inscription of the QRS Loop
68 Cases

Direction	Frontal	Sagittal	Horizontal
Anticlockwise	45	61	65
Clockwise	9	2	0
Figure-of-eight	14	5	3

Direction of the Long Axis of the QRS Loop.—A histogram of the long axes of the *QRS* loops as seen in the three projections is shown in Figure II. It is compared with a histogram of these axes in the 68 subjects of the normal series which were obtained by electronic synthesis. It will be seen that the distribution in the hypertensive patients is displaced to the left in the frontal plane ("left axis deviation"). In the sagittal plane there are two peaks in the frequency distribution. This is an expression of the fact that in this plane the longest axis is often not the projection of the true spatial long axis of the loop, which runs to the left and therefore towards the observer, but is a second axis directed up and back.

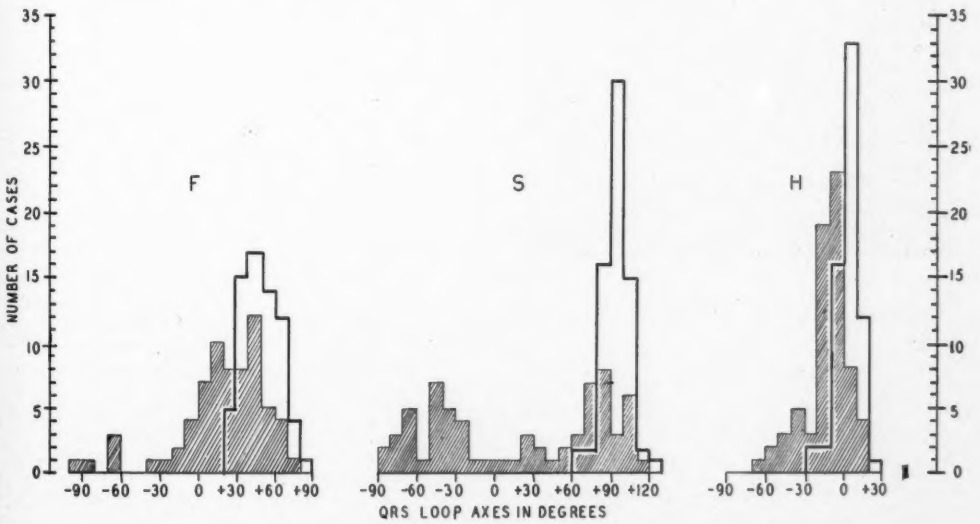

FIGURE II
Histograms showing the frequency distribution of the *QRS* axis angles in the frontal (*F*), sagittal (*S*) and horizontal (*H*) planes. The heavy lines indicate the distribution in a series of normal subjects and the shaded areas that observed in the present series.

Though not the spatial axis, it has been found useful to record this apparent axis in the sagittal plane (Figure X). In the horizontal plane, the long axis may be displaced a little further back than normal.

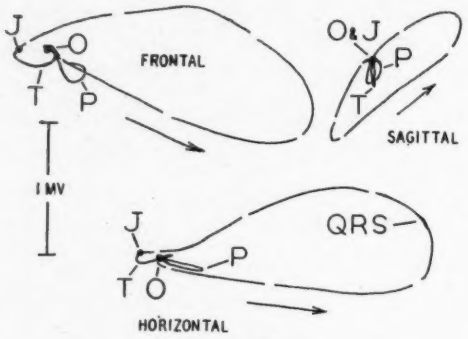

FIGURE III

Traced drawings showing "horizontal loop" type of VCG with a *J*-shift. Time markers 0·01 second apart.
In all illustrations the component parts of the VCG are indicated as follows: *P*=auricular complex; *QRST*=ventricular complex; *O*=origin; *J*=junction of *QRS* and *T* components. The arrow indicates the direction of inscription. Interruptions on the trace indicate time markers

Contour of the QRS Loop.—The normal *QRS* loop shows typically a small initial deflection or "crochet" directed to the right and forwards. A smooth centrifugal limb then passes down and to the left to the apex of the loop, and this is

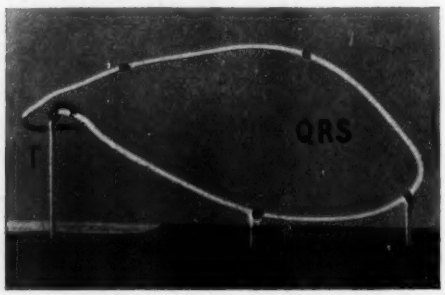

FIGURE IV

Photograph of a model of the VCG shown in Figure III viewed from the front, above the origin and slightly to the (model's) right

followed by a smooth centipetal limb, with perhaps a second small deflection opposite in the direction to the main loop (terminal "crochet"). The loop is usually narrow, and the rate of inscription, slow at first, increases evenly, and decreases again without sudden changes. In contrast, the loops in this series are usually broader and more open, with irregularities of shape and often of the rate of inscription, especially along the centripetal limb. Certain general types of contour may be made out, although features of each may be combined in any one tracing (Table II).

1. The Horizontal Loop.—The first type may be called the "horizontal" loop (Figures III and IV). Although rather broader, it does not differ much in general shape from the

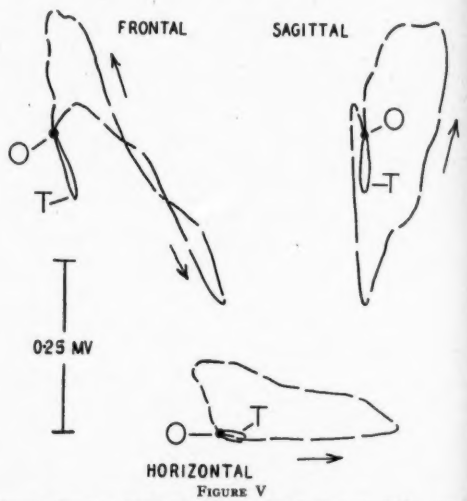

FIGURE V

Traced drawings showing "fling-up loop" type of VCG. Time markers 0·005 second apart

normal. Its main feature is its axis deviation "to the left" and often somewhat back. A horizontal element was seen in 20 cases of this series.

TABLE II

Types of QRS Loop

Direction	Number of Cases	
Horizontal	20	50
"Fling-up"	26	
Bizarre	15	
Backward	4	
Left bundle branch block	3	18
Right bundle branch block	1	
Normal	14	
Total	68	

2. The "Fling-up" Loop.—The most common type of abnormality, however, seen in 26 of 50 abnormal *QRS* loops, was a particular distortion of the loop (Figures V and VI). Although the initial crochet, the centrifugal limb and often the first third of the centripetal limb appeared normal, both in contour and in axis, there then occurred a change in direction

of the loop, its path travelling upwards and backwards to a point high above and behind the origin (*O*), sometimes a little to the right, before returning to *O*. This distortion was more than a prominent terminal crochet, starting as it did at some point along the centripetal limb, and often dominating the VCG picture. We have termed it the "fling-up" pattern.

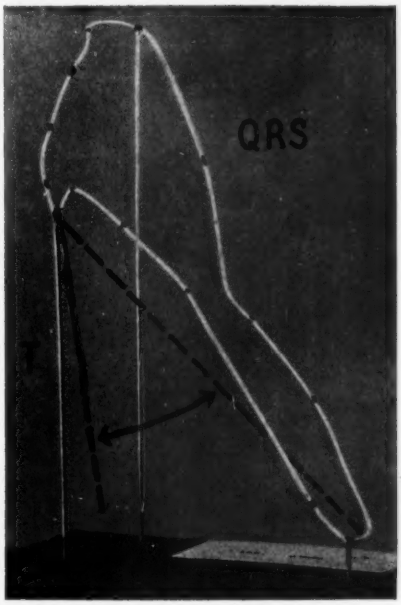

FIGURE VI
Photograph of a model of the VCG shown in Figure V viewed from in front, above the origin and slightly to the (model's) left. *P* loop has not been reconstructed

3. Bizarre Loop.—A third general abnormality of the *QRS* loop we have described as "bizarre" (Figures VII and VIII). Although the general orientation of the loop may resemble either of the two previous types, its path is irregular in direction and sometimes in rate of inscription. This often produces a grotesquely distorted figure. It occurred in 15 cases.

4. The Backward Loop.—In four loops the main abnormality was a striking backward shift of the loop axis beyond normal limits.

In three cases, the contour was typical of that seen in left bundle branch block. The loop was directed backwards at an angle of about 45°, the track being first somewhat downwards, then upwards at the end of the centrifugal limb and very slightly forwards. It then sloped down forwards and inwards past the origin to a displaced *QRS-T* junction (*J*).

In one case there was the contour of right bundle branch block, with a normal centrifugal limb and first half of the centripetal limb, followed by a slower secondary loop directed to the right and slightly forwards.

In the 64 cases without bundle branch block, the initial crochet was normal in 50, unidentifiable in six, possibly abnormal in seven, and definitely abnormal in one.

The centrifugal limb of the *QRS* loop was directed to the left of the mid-line in all cases.

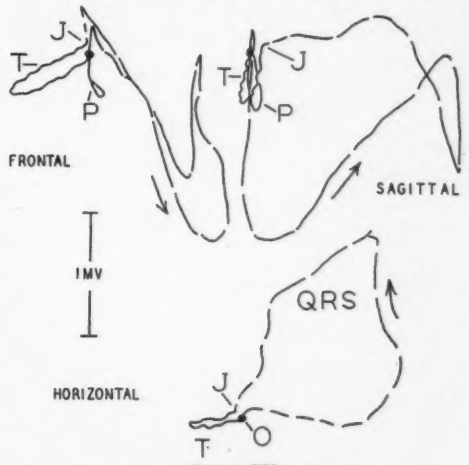

FIGURE VII
Traced drawing showing "bizarre loop" type of VCG with small *J*-shift. Time markers 0·005 second apart

In 52 it was directed below the horizontal, in six horizontally, and in six above the horizontal. In 12 it was directed in front of the coronal plane, in 25 behind it, and in the remainder more or less directly to the left in this plane (Table III).

TABLE III
Direction of Centrifugal Limb of QRS Loop
64 Cases

Direction	Number of Cases
Left	64
Down	52
Horizontal	6
Up	6
Forward	12
Back	25

The centripetal limb is difficult to analyse, because of its great variation. It was in this limb that the chief distortion occurred, especially the "fling-up" pattern. Even when undistorted, it always curved more posteriorly than in

normal cases on its path to the origin, producing a broader, more open contour.

Displacement of the QRS-T Junction.—The point where the *QRS* loop becomes continuous with the remainder of the *QRST* complex is known as *J*, the junction where the rapidly inscribed component suddenly slows

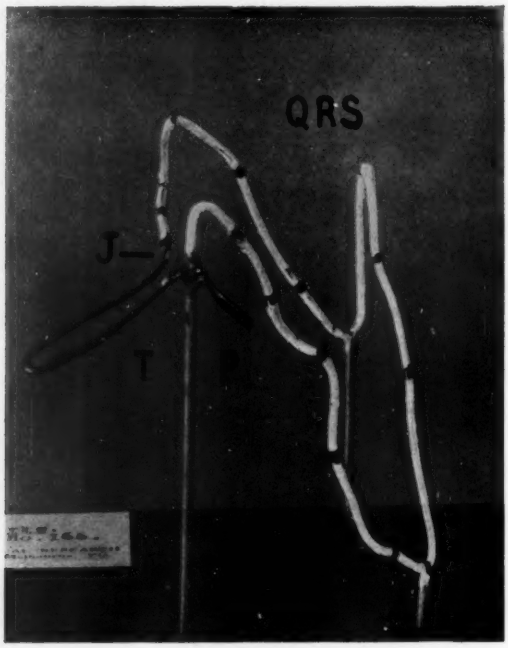

FIGURE VIII
Photograph of a model of the VCG shown in Figure VII, viewed from the front, slightly above and to the (model's) right of the origin

(Figure IX). In normal subjects, *J* coincides almost exactly with *O*, the origin of the *QRS*. A shift of *J* of anything more than minor degree is abnormal. It occurred in 42 of the 65 cases in which it could be determined. The direction of shift is of some interest; it will determine in which scalar electrocardiographic leads the shift will best be seen as an *S-T* segment depression. In various combinations the shift in the cases without bundle branch block was directed as follows: to the right in 37 cases, forward in 15 and back in two, up in 18 and down in two (Table IV). In the cases of left bundle branch block pattern there was a *J*-shift to the right, forwards and upwards; in the case of right bundle branch block the *J*-shift was to the right and upwards.

Grishman and Scherlis attach significance to the direction of the *J*-shift in the differentiation of left ventricular hypertrophy from left bundle branch block. They found a shift to the right

TABLE IV
Direction of Displacement of J *Relative to* O
61 Cases

Direction	Number of Cases
Right	37
Forward	15
Back	2
Up	18
Down	2
No displacement..	13

and up in 11 cases of left ventricular hypertrophy, but to the right and down in cases of

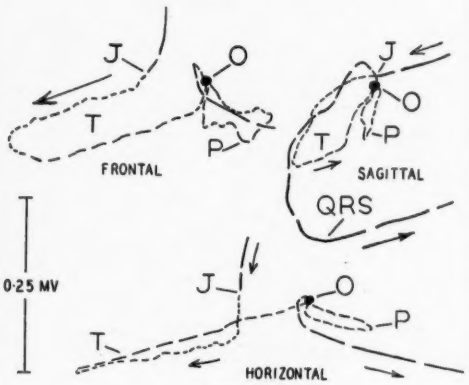

FIGURE IX
Traced drawings showing *J*-shift and details of *T* and *P* in VCG. Time markers 0·005 second apart

left bundle branch block. This, however, is not in accord with our findings.

JT Component of the Ventricular Complex.—In cases in which there is no *J*-shift, the electron beam pauses at the end of the *QRS* loop, at or about the origin, before inscribing the remainder of the ventricular complex, which takes the form of a loop. In cases in which there is a *J*-shift, however, such a loop is not observed, and the *JT* component is an open figure rather than a closed loop. It is roughly *U*-shaped, although one of the limbs may be longer than the other. The body of the *U* may be directed away from the main *QRS* loop; but this is not invariable, for in a few cases it had nearly the same direction as the *QRS* loop, as in the case of the normal subject—that is, the *QRS-T* spatial angle was normal. This occurred in four cases in which a *J*-shift was present.

The rate of inscription of the *JT* segment was always slow at first, with a faster final limb, as seen in the normal VCG (Figure IX).

QRS-T Spatial Angle.—The *QRS-T* spatial angle is the angle in space between the long axis of the *QRS* component and that of the *JT* segment (*T* loop), as measured from the origin. In the series of normal cases previously reported it did not exceed 30°. In the present series it exceeded that figure, often by a considerable amount, in 49 cases, in 36 of which there was also a *J*-shift. In the 13 cases in which a *J*-shift was absent, the *QRS* loop was abnormal in ten. There were thus three cases in which a *QRS-T* angle of over 30° was the only finding suggestive of abnormality. Grant *et alii* (1951) state that in normal subjects the *QRS-T* angle is usually less than 40°; it may be up to 50°, and in occasional cases more. An increase of the angle is often associated with advancing age. However, these three subjects were comparatively young, aged between thirty-seven and forty years, and their *QRS-T* spatial angles ranged from 120° to 180°, far beyond the usually accepted range of normal. As none was taking digitalis, we considered that this large angle represented definite abnormality.

An increased *QRS-T* spatial angle, a *J*-shift or a combination of both was present in 53 of the 63 cases in which both could be determined. Of the five remaining cases, one or other was determined in four and found abnormal in three. Thus, in 56 of 67 cases there was a *J*-shift or *QRS-T* angle abnormality.

Digitalis Effect.—The effect of digitalis on the VCG has been found to take the form of a *J*-shift, with a *JT* segment directed away from the main axis of the *QRS* loop at an angle approaching 180° when the effect is pronounced. Lesser degrees of digitalization may produce only a slight *J*-shift, leaving the *QRS-T* angle normal. This effect may have been responsible for the *J*-shift found in one patient taking the drug in whom no other abnormality was present. Another patient had in addition an increased *QRS-T* angle, but as the *QRS* loop was normal, this too may have been a digitalis effect.

Fourteen patients in this series were taking digitalis. In all some degree of *J*-shift was present. Eleven also had an increased *QRS-T* spatial angle, in two the angle could not be determined, and in one it was normal—the first case mentioned above.

Exactly similar abnormalities were noted in the larger group of patients with *JT* abnormalities who were not taking digitalis. Unfortunately, no certain way of distinguishing the two groups could be found.

TABLE V
Comparison of VCGs and ECGs

Observation	VCG	ECG
Normal	7	17
Abnormal	61	46
Total	68	63
17 subjects with normal ECG	Abnormal in 11 Normal in 6	—
J-shift and/or increased QRS-T angle in VCG[1]	Present in 56 Absent in 11	—
S-T and/or T changes in ECG[2]	—	Present in 46 Absent in 17

[1] 67 tracings examined.
[2] 63 tracings examined.

Comparison with Standard Electrocardiograms (Table V)

Routine standard electrocardiograms were recorded in 63 of the 68 cases, and of these 17 tracings were reported as normal, the remaining 46 showing the changes of left ventricular strain or preponderance. All the latter were associated with an abnormal VCG, but in two the *QRS* loop was normal. As both these patients were taking digitalis, it was thought that the *JT* and *T* abnormalities might have been due only to the effect of this drug.

Of the 17 patients having electrocardiograms regarded as normal, six had normal and 11 had abnormal VCGs. The abnormalities consisted in all cases of an abnormal position or contour of the *QRS* loop; in addition in seven cases there was an increase of *QRS-T* spatial angle. Five of these abnormal VCGs were found in the seven cases in which the electrocardiogram, although not considered diagnostic of left ventricular hypertrophy, showed left axis deviation.

The six remaining patients, together with one patient for whom an electrocardiogram was not available, provide a total of seven normal VCGs in the series of 68. In two other cases it is possible that digitalis accounted for the abnormalities found.

J-shift, or increase in the *QRS-T* spatial angle, or both, were shown in the VCG in 56 patients out of the 67 in which one or both of these factors could be determined, in contrast to *S-T* segment and *T* wave abnormalities in 46 of 63 electrocardiograms. *QRS* loop

abnormalities were found in four of the remaining 11 cases. In an additional subject whose *JT* segment could not be analysed there was also a loop abnormality. This makes a total of 61 abnormal tracings in 68 cases. Of 63 cases in which an electrocardiogram was taken, in 57 there was an abnormal VCG as against 46 in which the electrocardiogram was regarded as abnormal.

Correlation with Clinical Findings

An analysis of the groups with different types of *QRS* loop abnormality showed no correlation with the severity of the disease, as judged by the height of the blood pressure, and the presence of symptoms, of retinopathy or of a history of congestive cardiac failure. However, it was found that in an increased proportion of the severe cases (grades 4 and 5) there was a *J*-shift, and in an even greater proportion an increased *QRS-T* spatial angle. Thus, in 28 cases of 32 classed as grades 4 and 5 there was an increased *QRS-T* spatial angle, as opposed to 17 of 29 cases in grades 1 to 3.

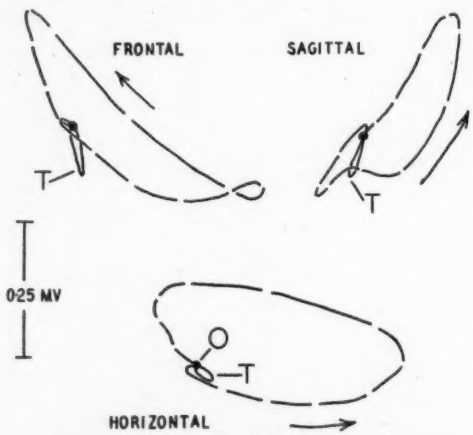

FIGURE X

Traced drawing of VCG showing "fling-up loop" in a patient in whom the scalar ECG (Figure XI) was considered normal

DISCUSSION

The picture seen in the majority of cases in this series is one of abnormality of the *QRS* component of the ventricular complex, either in its position or in its contour or both. This is combined in most cases with a *J*-shift or an abnormally large *QRS-T* spatial angle or both. The latter changes may occur independently of the exhibition of digitalis, although they may be indistinguishable from the effects of that drug.

The most common distortion of contour of the *QRS* component—the "fling-up" pattern—was a striking and easily discernible feature, whether grafted on a loop apparently normal for half to two-thirds of its duration, or combined with a horizontal or even a bizarre loop. This pattern has not been emphasized in the studies of left ventricular hypertrophy reported from other centres, yet it occurred in about half of the loops with *QRS* abnormality.

When the value of this method of recording the heart's electrical activity is discussed and compared with the standard electrocardiogram, it should be pointed out that the heart is giving out exactly the same electrical information to both recording machines. If the two types of machine are of equal quality, their relative value depends upon the ease of interpretation of the record obtained.

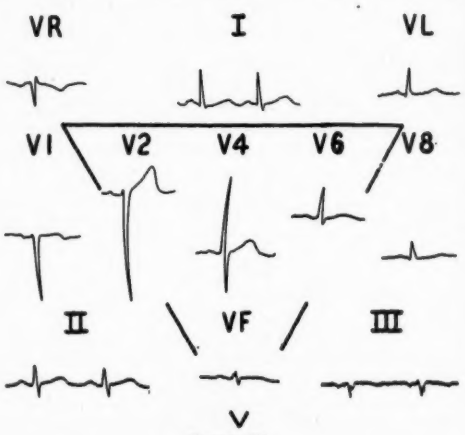

FIGURE XI

ECG of the patient whose VCG is shown in Figure X

Changes in the *S-T* segment and *T* wave of the electrocardiogram can be seen with relative ease. They were identified in 46 of 63 cases in this series.

However, analysis of *QRS* abnormalities in the electrocardiogram is more difficult. Criteria often adopted for this purpose are as follows:

1. The height of the main deflection in certain leads, referred to as "high voltage" and said to indicate left ventricular hypertrophy (Goldberger, 1949). Many factors may influence the height of recorded complexes, including the position of the heart relative to the recording electrodes, the resistances employed in the leads, and sometimes the skin resistance of the patient.

2. The timing of the waves of the *QRS* complex in certain leads, and especially the *Q-R* interval in chest leads over the left ventricle—for example *V*6 (Noth *et alii*, 1947). An adequate recording instrument is essential for the correct application of these rules. Owing to these factors, the interpretation of abnormalities of the *QRS* complex in the standard electrocardiogram is difficult and often uncertain.

On the other hand, most abnormalities of the *QRS* loop in this series were relatively easy to recognize. They were thought to be definitely present in 11 of the subjects passed as normal by the standard electrocardiogram (Figures X and IX). Moreover, the abnormalities of the *QRS* vector loop, especially the "fling-up" element, are most apparent in the sagittal projection, the longest axis of which is often in the region of −20° to −80°. However, as this projection is the least explored by conventional electrocardiographic leads, the "fling-up" is less readily appreciated by that method.

SUMMARY

Vectorelectrocardiograms recorded by electronic synthesis in 68 cases of left ventricular hypertrophy in hypertension are described. In general, the changes seen are as follows:

1. Abnormalities of the *QRS* component of the ventricular complex: (i) of position, especially horizontal rotation ("to the left") and back; (ii) of contour, especially a distortion upwards and backwards of the latter part or the whole of the centripetal limb of the loop—the "fling-up" type; sometimes a bizarre pattern is found.

2. A shift of *J*, the junction of the *QRS* component and the remainder of the ventricular complex.

3. Abnormalities of the *JT* segment, in particular of the spatial angle between this and the *QRS* loop.

Some or all of these may occur in combination; there are minor variations of the patterns.

The method appears to provide additional information in these cases about the electrical activity of the heart, because that activity is portrayed in a form in which recognition of the abnormalities is easier than in the conventional scalar electrocardiogram.

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We wish to express our appreciation and thanks to the many colleagues and assistants who have made this investigation possible.

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ABDOMINAL AORTOGRAPHY[1]

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SINCE the advent of the less toxic radio-opaque compounds, many of the objections against vascular radiography have been removed. Already cerebral and cardiac angiography have established themselves as essential diagnostic procedures, though abdominal aortography as yet has not been widely accepted. It seems certain, however, that this is a safe and valuable adjunct to diagnosis in certain diseases of the kidney and of the aorta and its branches.

The procedure was described first by the Portuguese workers dos Santos, Lamas and Caldas (1929), and subsequently in America by Osorio (1933). Melick and Vitt (1948) were able to report from America three thousand abdominal aortograms. The first report in the British literature was by Griffiths (1950), and later Johnstone (1952) and Moore (1952) of Leeds published a comprehensive study of their experience.

TECHNIQUE

Of the various methods used for the introduction of the radio-opaque substance into the aorta, the one now universally favoured is the direct puncture of the aorta through the lumbar region.

The contrast medium we have used is 70% diodone solution. Many thousand intravenous and intraarterial injections of this substance have been given without any complication, and we have injected it directly into the renal artery and superior mesenteric artery without any ill effect. Johnstone (1952) and Moore (1952) have had the same experience. We use a test dose of one millilitre of 35% diodone solution intravenously for determining sensitivity in those patients who have not previously undergone excretion pyelography. Sodium iodide solution (80%) has been used by some workers but is painful on injection and there is some risk of iodism. Wagner and Price (1950) reported a case of thrombosis of the superior mesenteric artery following the use of this particular compound. "Thorotrast" is not recommended on account of its radioactivity.

[1] Received for publication on January 9, 1953.

The procedure is carried out under light "Pentothal" anæsthesia with local infiltration of the *musculus sacrospinalis* with 1% procaine solution along the track of the needle. Moore (1952) and others carry out the injection with local anæsthesia only in order to gain the cooperation of the patient, who holds his breath during the exposure of the cassettes. We have had no experience except under "Pentothal" anæsthesia, and note that Weyde (1952) considers that a better "nephrographic" effect is obtained when "Pentothal" is used. If the examination is for demonstration of the renal parenchyma, a preliminary bowel washout is advisable.

The aortic puncture is made by inserting the needle through the lumbar region eight centimetres to the left of the mid-line, in a direction upwards and inwards, first to strike the body of the vertebra and thence onwards to enter the aorta. The level of penetration of the aorta depends on the structure to be demonstrated, and must be determined in each case by taking a preliminary film with suitable siting marker.

The level of origin of the main vessels in the normal subject is as follows: (i) cœliac axis: upper border of twelfth thoracic vertebra; (ii) superior mesenteric artery: centre of twelfth thoracic vertebra; (iii) renal vessels: centre of first lumbar vertebra; (iv) inferior mesenteric artery: upper border of third lumbar vertebra; (v) bifurcation of aorta: fourth lumbar vertebra.

By means of a stainless steel number 16 standard wire gauge needle with Luer-Lok fittings, 14 centimetres long, 25 millilitres of 70% diodone solution are injected in two seconds or less, to obtain a "bolus" effect, and ensure that the contrast medium is not diluted too rapidly. A satisfactory film depends on the rapid injection of a suitable contrast medium.

The cassette changer holds ten 15 by 12 inch films, and as the changing mechanism is worked by hand, pictures can be obtained at any desired interval. Scatter has been lessened by a reticulated Lysholm grid, and a one millimetre aluminium filter is used. Exposure factors are 75 to 95 kilovolts, 100 milliamperes and 0·25 second.

Johnstone's (1952) graph of the average time of filling of the renal arteries and their branches has led us to expose one film during the injection, then two more films at half-second intervals. These should show the arterial and " capillary " phase of filling of any renal tumour. Three more films are exposed at intervals of one second or longer, to display the " nephrographic " effect. or observe transit of the contrast through the iliac vessels.

Difficulties

No difficulty in entering the aorta should be experienced if a sufficiently long needle is used. Just prior to making the pucture and whilst the tip of the needle is in the loose areolar tissues, a few minims of heparinized saline or procaine solution (1%) are injected through the needle to clear the lumen. There is no doubt when the aorta is penetrated. It has been found occasionally that all the contrast medium has gone into one or another vessel—for example, a renal artery or the superior mesenteric artery—owing no doubt to either direct penetration of, or proximation to, the origin of the lumen of that particular vessel. For this reason injection of heparinized saline is continued whilst the films are being developed. In the case of incorrect filling, the needle is completely withdrawn and the aortic puncture is made at another level.

Dangers

Injection into vessels other than the aorta is unlikely, once the aortic flow through the needle has been appreciated. Perhaps the greatest danger is the injection of the contrast substance in and around the aorta, owing to the needle's becoming dislodged during forcible injection. This can be obviated to a certain extent by suitable pressure tubing connecting the syringe to the needle. Moore (1952) reports that this results in severe pain for several hours. In the one case in which this has occurred in our series so far, the patient did not seem to be unduly disturbed. A considerable fall in systolic blood pressure occurred in two of our cases. Both patients were hypertensive.

Little trauma is caused by penetration of the aorta, and apparently no hæmatoma occurs on withdrawal of the needle. This has been demonstrated during the operation of lumbar sympathectomy carried out within two days of aortography in two of our cases, and has also been the experience of Goodwin, Scardino and Scott (1950) and of Smith, Rush and Evans (1951). The risk of injury to abdominal organs is negligible, as the needle is introduced through the paravertebral muscle mass (Figure I).

Seriously impaired renal or hepatic function is a contraindication to the examination, as is hypersensitivity to the contrast medium or the presence of an aneurysm of the abdominal aorta. Extensive calcification of the aorta is generally agreed not to be a bar.

INDICATIONS

While aortography is unlikely to become a routine diagnostic procedure, it is of special value in the elucidation of certain renal diseases.

FIGURE
Transverse section of the trunk at the level of the upper part of the body of the second lumbar vertebra viewed from above, showing the needle *in situ*

It is unquestionably the only method of diagnosis in certain diseases of the aorta and its branches.

Renal Abnormalities

After the injection into the aorta, the diodone is distributed rapidly in the various organs, which become radiographically visible. This distribution will, as has previously been indicated, depend on the level at which the injection is made. The resultant opacity of certain organs will provide a clear picture of their size, outline and uniformity of structure.

Thus the procedure becomes an ideal method of examination of the kidney, as one can obtain serial pictures of the origin, direction and number of renal arteries and their branches.

When the diodone is distributed in the arterioles, capillaries and venules of a kidney, the functioning excretory tissue becomes opaque. This is the commencement of the " nephrographic " effect. Shortly after this, the renal vein and its branches may become visible, but

the renal substance remains opaque because of the secretory function of the renal tubules. As the concentration of the diodone rises in the calyces and pelvis, a pyelogram can be obtained. A larger amount of diodone may enter one renal artery, and the " nephrographic " effect on this kidney may be greater. Areas of

FIGURE II
Aortogram. Simple cyst in the upper pole of the left kidney. Arterial phase

destroyed renal tissue will not exhibit this " nephrographic " effect, and the arterial branches to such an area will be noticeably truncated or displaced.

In malignant disease of the kidney, films in the arterial phase of filling show a meshwork of newly formed abnormal vessels, which differ in distribution, form and size from the normal. This is followed in a few seconds by irregular accumulation of contrast within the tumour, sharply demarcating it from the normal part of the kidney. The term " puddling " has been applied to this appearance. Later, while the normal part of the kidney may still show a " nephrographic " effect, the tumour area no longer contains diodone.

Weyde (1950) reported a series of kidney tumours; of 20 hypernephromata, a varying number of abnormal vessels could be demonstrated in 18 cases. In this same series, in 13 cases of solitary cyst of the kidney, it was possible to exclude a malignant tumour in 11 cases. A solitary cyst should not be diagnosed unless the deformity of the kidney pelvis and the arched deviation of the renal arteries surround a rounded area from which the " nephrographic " effect is absent.

Figure II depicts a solitary cyst in the upper pole of the left kidney. In the excretion pyelogram, a rounded tumour was seen projected over the upper pole of the left kidney, and there was a smooth displacement of the upper calyces, suggesting a tumour replacing but not invading the kidney substance.

The renogram (Figure II) shows truncation of the inter-lobar arteries supplying the upper pole of the left kidney, and these vessels are displaced downwards. There is a sharply demarcated rounded area in the upper half of the kidney which contains no contrast medium.

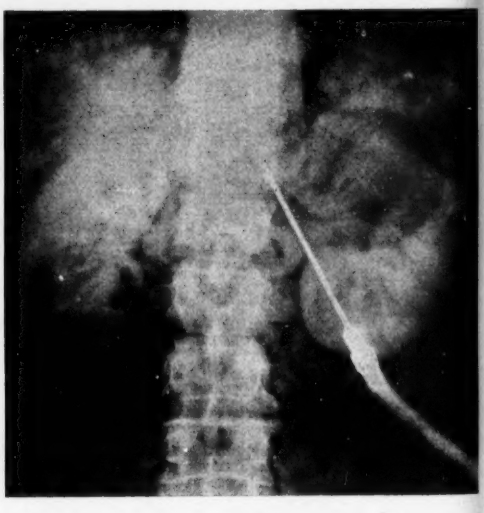

FIGURE III
Nephrogram. Simple cyst in the upper pole of the left kidney. The spleen, too, has become opaque

No abnormal vessels are present in this area, either in this illustration or in the " nephrographic " phase (Figure III).

Figure IV illustrates polycystic kidneys. The interlobar arteries are splayed and the branches are sparse. The renal shadows are enlarged, and on the right side multiple clearly defined cysts are seen surrounded by areas of

functioning renal tissue. The state of the left kidney has not reproduced well because of its poor function.

Figure V is that of a patient who, some years previously, was found to have a non-functioning right kidney by excretion pyelography. A more recent retrograde pyelogram revealed a small cavity extending from the upper minor calyx of the left kidney, and tubercle bacilli were present in the urine. The right ureteric orifice could not be located by the urologist. An aortogram was taken, and the first injection resulted in filling of the cœliac axis and the superior mesenteric artery only. The aorta was repunctured, and a second injection

FIGURE IV
Aortogram. Polycystic kidneys, arterial phase

disclosed two left renal arteries and a large solitary left kidney. Some contrast is present in the calyces, pelvis and ureter of the left kidney from the previous injection. The dark areas projected over the left renal substance are due to superimposed gas in the colon. No right renal artery or ectopic kidney could be demonstrated.

Vascular Lesions

With the changing views on obliterative arterial disease and the growing interest in reconstructive vascular surgery, arteriography is an essential preliminary to any subsequent surgical attack.

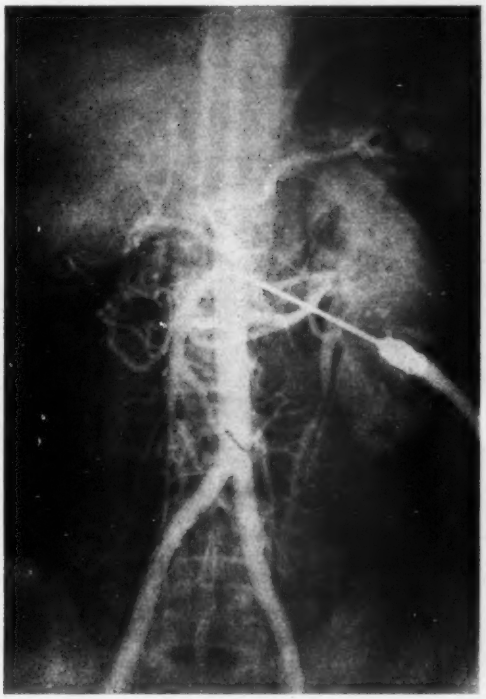

FIGURE V
Aortogram. Congenital absence of the right kidney, with two left renal arteries supplying a large solitary left kidney

With the technique we have developed, adequate filling may be demonstrated of the vascular tree, from above the cœliac axis to the origins of the *profunda femoris* arteries, and thus abnormal vessels, aneurysms, thrombosis and collateral circulation may be shown.

In Figure V is seen the appearance of a normal aorta and iliac arteries, with smooth, evenly tapering outline. In Figure II and Figure IV, whilst the outline of these vessels is smooth, some tortuosity is present.

Figure VI portrays extensive subintimal thickening in the lower part of the abdominal aorta, and the iliac and femoral arteries. The contour of the lower part of the aorta is uneven and similarly that of the iliac and femoral arteries. Cushions of thickened subintima,

aptly described by Lindbom (1950), project into the lumen of the vessels, resulting in a localized filling defect. There is almost complete obliteration of the lumen of the left common iliac artery just above its bifurcation, and the

FIGURE VI

Aortogram. Extensive subintimal thickening of the aorta and iliac arteries, and occlusion of the left femoral artery below the origin of the *profunda femoris*

left internal iliac artery is narrowed. The left femoral artery ceases abruptly just below the origin of the *profunda femoris*.

Figure VII is an aortogram illustrating Leriche's syndrome. The aorta tapers sharply below the origin of the renal arteries (and aberrant renal arteries are present on both sides), and terminates as a bulbous tip just below the upper border of the fourth lumbar vertebra. Anastomotic channels emerge from the bulbous tip like the snakes on Medusa's head. A leash of collateral vessels descends from the upper lumbar region behind the right kidney to the crest of the right ilium to anastomose with the deep circumflex iliac artery.

DISCUSSION

We consider that aortography by the translumbar route is a safe and relatively simple procedure, which, for its smooth performance, depends on the cooperation of a trained team. Several interesting cases from our small series have been presented in order to draw attention to the uses and potentialities of this method of examination.

As has been pointed out, aortography will frequently indicate the difference between hypernephroma and solitary cyst of the kidney.

In tuberculosis of the urinary tract, aortography is complementary to pyelography. The extent of an area of caseation may be recognized

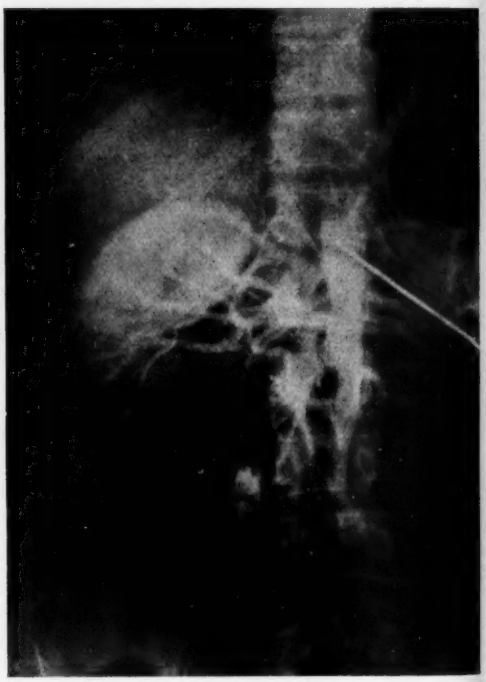

FIGURE VII

Aortogram. Lériche's syndrome. The lower part of the aorta is narrowed and terminates opposite the fourth lumbar vertebra as a bulbous tip, from which arise numerous collateral vessels. The lumbar-deep circumflex iliac anastomosis is visible above the right iliac crest

by the distortion of the arterial supply and subsequently the absence of a " nephrographic " effect in the affected area. This may be of considerable value to the surgeon in assessing the possibility of a successful segmental resection.

In hydronephrosis, an aortogram may be helpful in that it will give valuable evidence of

the functional state of the kidney by the size of the vessels supplying it and the "nephrographic" effect. Further, it may disclose an aberrant vessel as the cause of the hydronephrosis.

In congenital abnormalities of the kidney, as Moore (1952) suggests, it may settle the diagnosis as to whether there are two kidneys or one, or whether an abnormality in the pyelogram represents a horseshoe or non-rotated kidney. It may assist in treatment, perhaps to show if the blood supply to the kidney with a double pelvis is such that part of the kidney can be removed.

Aortography is the method of choice in assessing the extent of the disease of the aorta and its branches, and it is a necessary preliminary to a planned surgical procedure in obliterative vascular disease. It makes possible the recognition of aneurysmal dilatations, and of the extent of arterio-venous malformations.

The pattern of the circulation in vascular tumours of the parietes, such as osteogenic and retroperitoneal sarcoma and certain metastases, may be of help in arriving at a diagnosis. In one such instance a pattern of the abnormal vessels and a tumour "stain" enabled us to locate a phæochromocytoma. A detailed report of this case is being prepared for publication elsewhere.

It will be noted in several of the accompanying figures that the splenic artery is visible and that the spleen becomes uniformly opaque. The hepatic and gastro-duodenal branch of the hepatic artery fill well, and the filling of the mesenteric arteries is variable. The wall of the gut becomes visible in the later stages as its capillary bed becomes filled with diodone. In our series, the increase in density of the liver has not been comparable with that obtained after direct injection of diodone into the portal vein.

Aortography may be used as an alternative method to retrograde femoral arteriography to demonstrate the site of the placental sinusoids in certain cases of ante-partum hæmorrhage, when identification of the soft-tissue shadow of the placenta is unreliable.

We consider that abdominal aortography should be used more widely, as present day radiological techniques produce good angiograms, and frequently we are in the position of being unable to interpret them adequately. As in cerebral and cardiac angiography, the more frequently abdominal aortography is employed, the more its potentialities will increase and the interpretation become more accurate.

SUMMARY

The history and technique of abdominal aortography are briefly described. Attention is drawn to some of the difficulties and dangers of the procedure. Some illustrative cases have been presented, and other applications of abdominal aortography have been mentioned.

ACKNOWLEDGEMENTS

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STUDIES IN MITRAL STENOSIS

I. THE DYNAMICS OF THE CIRCULATION [1]

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In this and the succeeding paper we shall review the material relating to a group of 57 cases of mitral stenosis selected from 250 patients with rheumatic heart disease seen in this Institute during the last two years. The 57 patients were selected as having predominantly mitral stenosis on the following clinical evidence: (i) a low rumbling diastolic murmur following the third sound or opening snap, usually with presystolic accentuation in those patients with sinus rhythm; (ii) a loud first sound at the mitral area; (iii) a normal or, more frequently, a diminished left ventricular impulse to palpation; (iv) absence of left ventricular preponderance in the electrocardiogram; (v) slight to moderate enlargement of the left auricle on fluoroscopy.

In 18 cases, a grade I to II mitral systolic murmur was heard, and in six a grade I basal diastolic murmur was the only evidence of aortic incompetence. In seven cases a basal diastolic murmur was attributed to pulmonary incompetence (Graham Steell, 1881). Forty-eight of these patients were submitted to mitral valvotomy, and in no instance was the surgeon able to detect significant mitral regurgitation. Three patients have died (one post-operatively), and pure mitral stenosis was found at autopsy.

Clinical Material

There were 14 males and 43 females. The ages ranged from nineteen to fifty-four years, with a mean of thirty-three years. Sinus rhythm was present in 44, auricular fibrillation in 12 and impure flutter in one. The cases were grouped into functional classes as follows; Class II: symptoms on moderate exertion (14 patients); Class III: symptoms on slight exertion (26 patients); Class IV: symptoms on the slightest effort or at rest (17 patients).

This somewhat arbitrary grouping corresponds fairly well with that recommended by the New York Heart Association (1945) but the series lacks patients in the milder grades of Class II and the more severe grades of Class IV, who are unsuitable for mitral valvotomy. The series is also weighted by a disproportionate number of patients with extreme pulmonary hypertension.

In cases 29, 40, 42, 44, 45, 47, 49 and 55 there was a history of congestive cardiac failure, but only one patient (Case 55) had œdema at the time of study. At the time of study all the patients with auricular fibrillation and most of the more incapacitated patients with sinus rhythm were taking digitalis. Some were also being given mercurial diuretics. There is evidence that cardiac glycosides have no consistent effect on pressure in the right side of the heart or on blood flow in patients with mitral stenosis and sinus rhythm not in failure, and no account has been taken of the effects of these drugs (Harvey *et alii*, 1951; Bloomfield *et alii*, 1952). More recently Ferrer *et alii* (1952) have shown that digitalis may affect left ventricular performance in patients with severe mitral valve disease, but their findings do not materially affect the arguments of this paper.

We shall now consider in detail the dynamics of the circulation and conclude with a brief reference to the application of the findings to the question of mitral valve surgery.

Methods

As far as possible these patients were studied in the basal state. Every effort was made by explanation and rehearsal to dispel anxiety, and only a few were given a sedative. After the introduction of an indwelling arterial needle (Cournand type) into a brachial artery, cardiac catheterization was carried out in the usual way by the use of a single or double lumen catheter. The catheter tip was advanced directly to the pulmonary "capillaries" (Hellems, Haynes and Dexter, 1949) under fluoroscopic control, the position being confirmed

[1] Accepted for publication February 13, 1953.

by the following features: (i) wedging of the tip so that it was influenced by respiratory movements and not by arterial pulsation or gentle traction on the catheter; (ii) difficulty in withdrawing blood which, if obtained, was obviously arterialized, though not analysed as a routine; (iii) absence of pulmonary arterial characteristics in the manometric tracing. The patient was then allowed to rest for ten minutes. Pulmonary "capillary" and pulmonary artery pressures were recorded either simultaneously or in rapid succession. A Douglas bag was then connected, and, after a few minutes of adaptation, expired air was collected for four minutes. Midway during the collection arterial blood and mixed venous blood from the pulmonary artery were drawn simultaneously and stored anaerobically under oil in the refrigerator. The pressures were again recorded, and after a short rest the studies were repeated during exercise which took the form of leg raising in the recumbent position 24 or, less frequently, 30 times a minute. Pressures were recorded at half-minute intervals during the exercise. Expired air was collected in the second and third minutes, and simultaneous blood samples were again taken at rest during a four-minute period. If, as in the majority of cases, a single lumen catheter was being used, exercise was again performed at the same rate with the catheter in the pulmonary capillaries, and the pressure was recorded as before. Oxygen consumption, estimated in a small number of these cases, showed very close agreement for the two periods of exercise. After a second recovery period the catheter was withdrawn to the right ventricle and right auricle, where pulse and mean pressures were recorded. A number of these patients also carried out exercise with the catheter in the right auricle and pressures were recorded.

In five patients exercise was performed for five minutes, and pressures and flows were estimated in both the second and third and the fourth and fifth minutes (Table I). There was no consistent difference in the results for the two periods of exercise, and it can be assumed that at the slow rate of exercise used, the patients were close to a "steady state".

TABLE I.

The Results Obtained on Five Patients with Mitral Stenosis, Three of them After Operation, Who were Exercised for Five Minutes. Cardiac Index was Determined During the Second and Third and the Fourth and Fifth Minutes of Exercise at a Steady Rate.

Patient's Initials.	Case Number.	State.	Arterio-venous Oxygen Difference. (Volumes *per Centum*.)	Oxygen Consumption. (Cubic Centimetres per Square Metre per Minute.)	Cardiac Index. (Litres per Squate Metre per Minute.)	Mean Pulmonary Artery Pressure. (Millimetres of Mercury.)	Pulse Rate. (Beats per Minute.)
A.K. (S.R.)[1]	10	R.[1]	3·5	93	2·7	30	100
		E.[1]	6·0	249	4·2	42	120
		E.	6·3	247	4·0	43	120
		R.	3·1	97	3·1	25	95
C.R. (S.R.)	21	R.	3·6	117	3·2	42	52
		E.	6·5	260	4·0	62	107
		E.	6·0	241	4·0	60	94
P.M. (Post-operative—A.F.[1])	22	R.	4·1	150	3·3	13	90
		E.	6·6	287	4·4	57	120
		E.	6·9	300	4·4	56	115
		R.	4·3	153	3·5	17	94
R.W. (Post-operative—A.F.)	33	R.	5·2	113	2·2	20	70
		E.	8·8	270	3·1	40	110
		E.	9·9	280	2·8	40	110
		R.	5·3	117	2·2	18	75
S.M. (Post-operative—S.R.)	38	R.	4·3	132	3·1	42	84
		E.	7·9	317	5·3	57	120
		E.	8·3	324	5·6	52	120
		R.	5·1	125	3·4	38	95

[1] R.=rest, E.=exercise, S.R.=sinus rhythm, A.F.=auricular fibrillation.

Blood samples were analysed for oxygen in the manometric Van Slyke apparatus (Van Slyke and Neill, 1924). Duplicate analyses were not made unless they were considered necessary. In this laboratory duplicates usually check to within 0·2 volume *per centum* or better. The oxygen capacity of arterial samples was determined on blood rotated gently for ten minutes at room temperature in a tonometer. The corrections of Roughton, Darling and Root (1944) were not applied. The volume of expired air was measured in a wet type gas meter and corrected to standard temperature and pressure. The air was analysed for oxygen and carbon dioxide in a micro-gas analyser

TABLE II.[a]

Case Number.	Age. (Years.)	Sex.	B.S.A. M^2.	Rhythm.	Mitral Valve Area. ($cm.^2$).	Arterial Blood.			A-V O_2 Difference. (Volumes *per Centum*.)	Ventilation. (Litres per Minute.)	$O_2/M^2/min.$ Cubic centimetres.	Cardiac Index. (litres per M^2 per Minute.)	Pulse Rate.	Stroke Index. (Cubic Centimeters per Beat per M^2.)	P.A. Pressure. (Mms. of Mercury.)			P.C. Mean Pressure. (Mms. of Mercury.)	PA.-PC Gradient. (Mms. of Mercury.)	Right Auricular Mean Pressure. (Mms. of Mercury.)	BA Mean Pressure. (Mms. of Mercury.)	Diastolic Filling Period. (Seconds per Minute.)	Resistances.		Right Ventricular Work. (Kilogram metres/min./M^2.)
						$(O_2$ Content. Volumes *per Centum*.)	O_2 Saturation Percentage.								Systolic.	Diastolic.	Mean.						P.A. Dynes second $cm.^{-5}$.	Total Pulm. Dynes sec. $cm.^{-5}$.	Elasticity. Dynes $cm.^{-5}$.	
					$4-6^b$				$4\cdot0^b$			$3\cdot0^b$	75^b	43^b			$8-15^b$	$5-10^b$	$3-10^b$		8^b	36^b	150^b	250^b	700^b	$0\cdot5^b$
1	35	M.	1·92	S.R.	3·8	19·2	98		4·1	4·8	119	2·9	75	39	17	5	9	5	4	−1			35·1	97	195	498	0·43
						19·8			7·0	14·6	275	3·9	97	46	36	14	25	14	11				116	263		
2	37	F.	1·54	S.R.	2·8	18·3	96		7·3	12·2	341	4·7	70	43	45	20	30	10	20				33·0	246	369	848	
						18·3			7·6	12·2	137	3·1	70	46	50	30	34	11	5	1	75	38·2	83	266	152	0·39
3	29	F.	1·50	S.R.	1·7	15·0			3·7	5·6	238	3·1	125	33	45	26	37	28	9	2		33·9	118	485		
						15·4	96		5·1	14·6	236	2·8	92	30	38	12	18	12	6	2	62	38·0	87	313	456	0·61
4	25	F.	1·58	S.R.	1·5	17·0	97		3·9	5·5	258	3·1	120	26	57	28	37	18	30	2	2	38·7	215	461	604	
						18·3	97		8·4	12·5	234	2·8	82	34	55	18	30	16	14	2		28·6	286	787	936	0·95
5	26	F.	1·66	S.R.	1·4	14·6	100		4·0	4·6	214	2·8	136	31	103	44	66	42	24	5	6	36·0	63	235	142	
						15·3	98		7·6	9·0	308	4·2	75	45	26	13	15	11	4	8	78	36·0	139	416	333	
6	37	F.	1·51	S.R.	1·4	17·8	98		5·9	13·5	190	3·4	90		37	19	23	15	8	3		35·6	416	749	1423	1·62
7	40	F.		S.R.	1·3	17·3	96		4·7						65	26	45	20	25		78	37·7	300	937		
8	25	M.	1·77	S.R.	1·3	19·0			8·0	7·1	133	2·7	150	31	110	55	75	35	40				697	1225	1·43
						19·5	93		8·2	14·7	293	3·6	86	24	55	30	42	17	25	3	82	35·6	415	697	0·92
9	39	F.	1·80	S.R.	1·3	18·9	97		4·5	7·2	120	2·7	79	34	70	30	42	25	17	0	74	32·6	124	444	428	2·34
10	41	F.	1·55	S.R.	1·2	18·9			3·6	3·6	93	2·7	90	30	36	16	25	18	7	2				529	448	1·06
						17·7	95		6·5	9·0	249	4·2	120	35	58	24	43									
11	22	F.	1·52	S.R.	1·2	18·0	94		6·4	6·0	123	2·8	90	31	40	23	30	12	14	2	80	33·7	213	533		
						17·8	95		6·4	17·6	293	4·4	128	34	60	33	45	31	14	2	80		167	537		
12	20	F.	1·64	S.R.	1·1	18·2			8·9	5·6	119	3·1	90	34	53	28	37	20	17	−2	92	36·6	272	591	597	1·64
						18·8	94		8·9	14·2	312	3·9	120	32	80	43	54	40	14	−2	108		175	674		
13	39	F.	1·52	S.R.	1·1	16·7	90		4·0	4·9	121	3·0	85	35	40	20	27	16	11	−2	90	38·7	335	480	736	1·18
						17·0			8·1	9·6	308	3·9	110	35	57	26	40	28	12				165	552		
14	27	F.	1·56	S.R.	0·9	17·4	95		3·6	4·9	99	2·7	70	39	50	24	35	20	15	0	80	39·4	281	562	546	1·29
						15·4	95		9·4	17·6	300	3·2	120	27	108	55	75	45	30	5			480	1200		3·04
Mean					1·5				4·0	5·3	117	2·9	83	35	43	19	28	16	12	0·5			248	459	739	
									7·3	13·8	284	3·9	123	32	69	35	51	33	18				265	657		

Class II.

15	42	M.	1·75	A.F.	1·4	18·3	92		4·8	6·4	121	2·5	120	21	40	20	25	15	10	1	85	36·6	282	454		
						08·6	91		9·9	13·9	274	2·8	144	19	55	30	41	31	10				167	682		1·14
16	36	M.	2·06	S.R.	1·2	17·4	96		7·0		274	3·1	70	39	65	25	40	15	25	0		35·6	487	780	633	1·00
17	27	F.	1·51	S.R.	1·2	16·0			7·3	4·0	127	3·2	100	32	56	18	25	18	6		97	33·6	213	693		
						17·0	96		7·4	15·0	103	3·1	125	30	36	25	41	32	9	0		30·5	114	520		
18	39	F.	1·56	A.F.	1·1	18·1			4·7	5·4	306	2·3	110	21	76	30	44	15	29	0			658	1034		
						18·5	90		10·6	12·8	228	2·3	145	15	102	40	82	30	52	2	70	34·9	1223	1928	545	0·99
19	37	F.	1·49	S.R.	1·1	15·1	98		3·9	5·9	105	2·7	70	39	45	22	29	16	13	2	70		260	579		
						16·2	98		7·5	15·4	223	3·0	110	29	70	35	51	30	21		70		373	906		
20	38	F.	1·57	S.R.	1·1	15·4	95		4·1	8·1	131	3·0	105	29	50	27	36	20	16	0	115	37·0	316	569	1311	
						15·7	97		8·2	14·4	310	4·1	145	28	85	54	60	30	30	3	84	42·0	375	750		1·48
21	25	F.	1·61	S.R.	1·0	18·1			3·6	14·7	117	3·2	70	46	60	25	37	22	15				231	569	539	
						18·4	95		8·2	18·0	260	4·0	115	35	102	72	66							812		
22	33	F.	1·62	S.R.	1·0	15·8			4·5	6·4	150	3·6	86	42	77	28	48	27	21	1	88	37·8	305	697		
						16·2	91		8·4	14·1	329	4·0	143	28	131	41	84	59	20	2	90	24·0		1049		
23	35	F.	1·76	S.R.	1·0	16·4	96		4·1	12·4	140	3·4	103	33	70	36	50	30	20	2	90	38·5	271	678		
						16·4	96		7·2	28·1	284	3·9	140	28	76	40	57							660	616	1·26
24	47	F.	1·49	S.R.	1·0	15·1	95		3·5	3·9	100	2·9	79	37	47	21	34	22	12	2	92	35·4	223	1483		
						16·0	96		12·4	25·0	250	2·9	150	20	110	63	82	46	36				658			

Class III.

23	32	F.	1·64	S.R.	0·9	17·8	96		4·4	5·8	118	3·7	73	30	38	16	28	23	17	8	104	39·2	309	727	739	1·40
						17·6	95		5·9	9·3	220	3·2	120	28	90	46	60	40	20				313	940		
26	37	F.	1·73	A.F.	0·9	18·4			5·9	9·3	131	2·8	103	21	40	26	30	23	9	2	80	34·8	189	831	301	0·84
						18·6	94		8·6	25·9	219	2·5	130	19	55	30	47	40	21	2				834		1·53
27	36	F.	1·40	S.R.	0·9	14·1			4·5	5·6	128	2·9	78	37	49	30	37	24	13	2	90	35·2	260	734	365	1·38
						14·8	99		6·2	14·3	205	3·3	96	34	60	37	46			2	92			799		

24	47	F.	1·49	S.R.	1·0	15·1 16·0	95 96	3·5 9·3	3·9 12·4	100 280	2·9 2·9	79 150	37 20	47 110	21 63	34 82	22 46	12 36	2	92	33·4	653	1489			
23	32	F.	1·64	S.R.	0·9	17·8 17·6	96 95	4·4 7·1	5·8 9·6	118 220	2·7 3·1	75 110	36 28	58 90	36 46	40 60	23 40	17 20	2	104	39·2	309 313	727 940	739	1·40	
26	37	F.	1·73	A.F.	0·9	18·4 18·6	94	5·9 8·6	9·5 25·9	131 219	2·2 2·5	103 130	21 19	40 55	26 40	30 47	21	9	2 2	80	34·8	189	631 854	301	0·84 1·53	
27	36	F.	1·40	S.R.	0·9	14·1 14·8	99	4·5 6·2	5·6 14·3	128 205	2·9 3·3	78 96	37 34	49 60	30 37	37 46	24	13	2 2	90	35·2	260	739 799	365	1·38	
28	28	M.	1·88	A.F.	0·9	18·9 19·0	95 96	5·5 9·0	5·2 10·1	114 221	2·1 2·5	55 80	38 31	30 60	15 30	20 40	14	6	2	95 106	44·8	123	410 695	151	0·51	
29	19	F.	1·62	S.R.	0·9	15·0 15·8	94	4·7 8·5	4·7 13·3	129 243	2·7 2·9	83 143	33 20	70 97	30 52	46 72	22 48	24 24	2	90	36·8	436 417	836 1251	1311	1·62	
30	19	M.	1·7	A.F.	0·9	16·8 17·3	96	5·0 7·6	5·0 14·6	120 242	2·4 3·2	75 120	32 27	40 75	20 48	28 60	18 39	10 21	0	87	42·6	195 311	546 888	245	0·91	
31	38	F.	1·49	A.F.	0·8	17·3	96	4·0	4·4	95	2·4	87	28	46	21	27	17	10	5	87	36·8	228	617	641	0·72	
32	42	M.	1·70	S.R.	0·8	16·8 17·7	97	4·9 8·7	6·3 15·1	128 230	2·5 2·6	87 127	29 21	65 93	24 40	43 66	25 47	18 19	2 7	73	38·7	347 338	818 1174	1226	1·39 2·08	
33	39	M.	1·80	A.F.	0·8	17·6 18·1	94	6·2 10·4	5·0 13·6	103 289	1·7 2·8	60 83	28 33	68 116	28 46	38 73	18 38	20 35	3	94	36·0	533 560	1013 1167	1269	0·81	
34	25	F.	1·48	S.R.	0·8	17·3 18·2	96	4·7 8·5	4·8 10·7	108 206	2·3 2·4	86 136	27 18	70 105	33 50	45 71	23 36	22 35	0	90	30·7	533 777	1090 1577	1645	1·41	
35	36	F.	1·52	S.R.	0·7	17·3 17·4	90	5·0 8·1	5·3 12·4	108 253	2·2 3·2	143 165	15 19	60 83	18 25	35 50	25 41	10 9	−1	78	34·3	242 150	848 833			
36	43	M.	1·64	S.R.	0·7	20·9 22·2	95 95	6·5 13·2	6·2 17·8	121 295	1·9 2·2	74 130	26 17	60 140	30 75	38 105	16	22	1 18	84 110	42·3	567	979 2268	991	0·95 4·38	
37	24	M.	1·95	S.R.	0·7	19·6 20·3	95 95	5·9 12·8	4·4 17·4	126 345	2·2 2·6	83 130	27 20	78 135	43 80	57 105	28	29		85 84	39·1	552	1083 1614	954	1·80	
38	33	F.	1·51	S.R.	0·6	18·8	72	8·0	8·2	158	2·0	160	13	115	64	86	35	51			28·8	1359	2292	6016			
39	42	F.	1·44	S.R.	0·6	14·9 15·5	94 94	5·8 10·1	4·8 11·9	108 225	1·9 2·2	66 112	29 20	53 106	22 56	35 69	17 32	18 37	4	72 82	39·6	533 799	1036 1723	1251	0·80	
40	47	M.	1·53	A.F.	0·5	17·6 17·9	95	6·5 10·3	5·6 12·3	106 226	1·6 2·2	75 95	21 23	42 86	20 32	28 54	18	10	5	80	41·9	322	902 1270	634	0·50	
Mean					0·9			4·9 8·9	5·7 14·5	116 254	2·4 2·9	79 117	30 25	54 90	26 48	36 64	20 39	16 26	2			366 476	781 1173	782		

Class IV.

41	37	F.	1·54	S.R.	1·2	19·3 19·5	97	4·1 7·0	6·7 9·2	113 185	2·7 2·6	94 110	29 24	86 117	32 47	52 73	20 30	32 43	2	71	38·6	683 859	990 1453	2807	1·83	
42	23	M.	1·76	S.R.	0·8	17·6 17·4	92 91	6·0 8·3	8·7 14·1	156 239	2·6 2·9	100 110	26 26	152 148	54 66	88 92	31	57	5 11	73	38·8	990	1529 1471	> 4630	2·93 3·19	
43	23	F.	1·71	S.R.	0·7	17·3 17·5	93 90	4·9 8·4	6·2 14·5	114 213	2·3 2·5	75 120	31 21	93 115	48 70	60 87	29	31	1	85	37·0	635	1229 1670	1229	1·84	
44	45	F.	1·58	S.R.	0·7	18·2 18·0	89 88	8·8 12·3	9·7 16·9	154 227	1·7 1·8	135 150	12 12	98 114	40 46	60 70	26	34	2 9	106	27·9	971	1776 1930	6813		
45	23	F.	1·31	A.F.	0·6	19·0	88	6·0		136	2·3	60	38	77	33	45	20	25	3	130	41·5	400	933	771	1·31	
46	39	F.	1·47	S.R.	0·6	18·5 19·1	98 97	6·3 12·5	7·6 16·2	143 300	2·3 2·4	105 135	22 18	102 135	53 61	78 91	32 40	46 51	5	91	34·1	1097 1158	1861 2066	3123	2·28	
47	27	F.	1·37	S.R.	0·5	14·5	76	7·4		138	1·9	160	12			57	18	39	6			1154	1688		1·32	
48	30	M.	1·71	A.F.	0·5	20·3 20·7	97	6·7 12·3	5·3 10·2	96 178	1·4 1·4	50 120	28 11	82 150	30 75	42 102	26	16	10 29	84 100	46·7	556	1460 3261	1032	0·57 1·39	
49	24	F.	1·30	S.R.	0·5	17·7 18·2	94 94	6·3 10·5	5·3 11·4	120 209	1·9 2·0	90 115	20 17	60 86	33 50	43 63	23 32	20 31	0	82	38·3	639 953	1374 1936	1229	1·11	
50	46	F.	1·49	A.F.	0·5	18·8 18·3	90 87	6·5 12·0	5·8 13·2	113 242	1·7 2·0	100 115	17 17	112 140	58 68	73 95	25 35	48 60	9	103 100	41·2	1475 1598	2243 2527	3333	1·48	
51	54	F.	1·55	A.F.	0·5	17·1 18·3	88 94	7·9 12·2	8·7 12·9	121 171	1·5 1·4	85 100	18 14	106 115	48 64	63 78	20	43	8	84	40·4	1494	2189 3808		1·12	
52	32	F.	1·70	S.R.	0·5	16·5 16·8	96	6·0 8·9		127 190	2·1 2·1	80 110	26 19			60 104	41	19	5		39·8	422	1332 2309		1·57	
53	22	F.	1·42	S.R.	0·4	23·1	96	8·5	7·1	120	1·5	74	20	120	50	73	20	53		100	40·5	1933	2662	4945	1·39	
54	39	F.	1·52	S.R.	0·4	19·2 19·6	96 94	7·4 11·4	5·3 14·2	122 247	1·6 2·2	81 115	20 19	116 140	50 70	72 97	28 32	44 65	8	96	40·5	1407 1574	2302 2349	> 3714	1·39	
55	34	M.	1·64	A.F.	0·4	17·9	91	10·2	7·0	137	1·3	85	15	132	52	80	35	45	18	93	38·4	1635	2907	> 5568	1·10	
56	43	F.	1·33	S.R.		20·7 20·1	96	9·0 13·4	10·1 9·4	129 166	1·4 1·4	70 90	20 16	100 125	40 56	60 77			3 15	101			2397 3239		1·09 1·18	
57	30	F.	1·45	S.R.		19·0 18·5	87 81	5·9 8·5	3·9 9·3	88 164	1·5 1·9	94 130	16 15	121 120	47 48	75 77			5	83 83	37·5		2775 2198		1·43	
Mean					0·6			6·4 10·4	6·7 12·2	120 209	1·9 2·0	86 114	23 18	102 126	45 61	64 86	25	39	4			1080	1806 2357	3518		

[a] Data obtained at cardiac catheterization top line resting, lower line exercising. Patients not in a basal state and those who did not exercise have been omitted in computing the means. Not all the patients who exercised did so with the catheter in the pulmonary capillaries, but the error arising from this in calculating the mean pulmonary artery-pulmonary capillary pressure gradient is negligible. Arteriolar resistances have been compiled from all the cases in which the calculation could be made.

B.S.A. = body surface area; O_2/M²/mm. = oxygen consumption in cubic centimetres per square metre of body surface per minute; P.A. = pulmonary artery; P.C. = pulmonary "capillary"; B.A. = brachial artery.

[b] Normal values.

(Scholander, 1947). Duplicates were required to check within 0·03 volume *per centum*. Conversion from expired to inspired air volume was made in the usual way. Cardiac output was determined by the Fick principle by the use of oxygen. There was no significant difference between the cardiac outputs determined before and after exercise, when pulse and pulmonary artery pressure had become stable. Agreement was usually better than in normal subjects, particularly when the output was low. We have therefore listed the first determination throughout. Body surface area was determined from the height and weight by the use of a nomogram derived from the formula of Dubois and Dubois (1915). Pressures were recorded by capacitance manometers (two channels) and a strain gauge (one channel) fed into a critically damped multichannel direct writing machine, whose pens had a resonant frequency in the range 50 to 60 cycles per second. Mean pressures were determined by electrical integration. Zero point for pressures was five centimetres below the angle of Louis.

Mitral valve area was calculated from the formula of Gorlin and Gorlin (1951) as follows[1]:

$$\text{MVA (cm.}^2\text{)} = \frac{\text{C.O. (c.cm. per min.)}}{31 \times \text{D.F.P.} \times \sqrt{\text{P.''C.''M.P.} - 5}}$$

There are theoretical objections to some of the assumptions made by these authors; but, provided mitral incompetence is not overlooked, the calculated valve areas agree well with the impression obtained by the surgeon at operation. It is apparent from the formula that errors are likely to be greater at the high valve areas and low capillary pressures. Resistances were calculated from the equation

$$\text{Flow} = \frac{\text{Pressure gradient}}{\text{resistance}}$$

as follows:

$$\text{P.A.R. (dynes sec. cm.}^{-5}\text{)} = \frac{(\text{P.A.M.P.} - \text{P.'' C.''M.P.}) \times 1332 \times 60}{\text{C.O. (c.cm. per min.)}}$$

$$\text{T.P.R. (dynes sec. cm.}^{-5}\text{)} = \frac{\text{P.A.M.P.} \times 1332 \times 60}{\text{C.O. (c.cm. per min.)}}$$

The assumptions on which these formulæ are based are discussed by Gorlin, Haynes *et alii* (1951). Elasticity resistance was calculated from the approximation suggested by Broemser and Ranke (1930) as follows:

$$\text{E.R. (dynes cm.}^{-5}\text{)} = \frac{\text{P.P.} \times \text{P.A.R.} \times \text{P.R.}}{\text{D.P.} \times \text{D.F.P. per minute}}$$

As an approximation of the work of the right ventricle we have used the following formula:

$$\text{Work} = \text{C.I.} \times \frac{(\text{P.A.M.P.} - \text{R.A.M.P.}) \times 13{\cdot}6}{1000}$$

kg. M. per min. per square metre.

This neglects the velocity energy, which on account of the lowered stroke volume and increased cross-sectional area of the pulmonary artery is probably even smaller in mitral stenotics than in normal persons. The formula thus represents pressure energy only, and because of the errors in the calculation of that fraction (Landowne and Katz, 1944) it seemed an unnecessary refinement to make a correction for the specific gravity of the blood. Right auricular mean pressure in this series has not differed from right ventricular end diastolic pressure by more than one or two millimetres of mercury, and so is an acceptable measure of presystolic pressure in the ventricle.

RESULTS

The results are set out in Table II.

Pulmonary "Capillary" Pressure

In Figure I are shown pulmonary "capillary" pressure traces in two cases of pure mitral stenosis. For comparison a direct left auricular trace in the second case is also shown. Because of the variability of the damping of left auricular pressure curves by the pulmonary capillary bed, it seemed unwise to place too much weight on the form of the "capillary" trace in studying events in the left auricle. There is evidence in mitral stenosis that the mean pressure is of the same order in the pulmonary "capillaries" and the left auricle (unpublished observations), and it has been assumed that these pressures are equal. At rest pulmonary "capillary" pressure showed a progressive increase from Class II to Class IV, the means for the

[1] The abbreviations used in the equations are as follows: M.V.A. = mitral valve area; C.O. = cardiac output; D.F.P. = diastolic filling period; P."C."M.P. = pulmonary "capillary" mean pressure; P.A.R. = pulmonary arteriolar resistance; P.A.M.P. = pulmonary artery mean pressure; T.P.R. = total pulmonary resistance; E.R. = elasticity resistance; P.R. = pulse rate; D.P. = diastolic pressure; D.F.P. = diastolic filling period; C.I. = cardiac index; R.A.M.P. = right auricular mean pressure; kg. M. = kilogram metres; P.P. = pulse pressure.

three groups being 16, 20 and 25 millimetres of mercury. On exercise the pulmonary "capillary" pressure rose in all patients, except in some with right ventricular failure.

Pulmonary Artery Pressure

The pulmonary artery mean pressure became higher with increasing severity of the disease. During exercise it rose still more, even when the cardiac index showed no significant change.

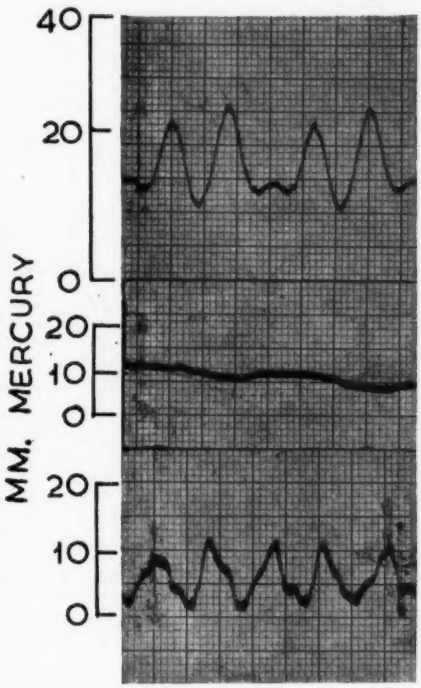

FIGURE I.

Pulmonary capillary traces taken in Case 5 (upper) and Case 6 (middle) to illustrate the great variation in contour due to damping. The lowest tracing was taken direct from the left auricle in Case 6 at operation.

In a few patients in Class IV with right ventricular failure the pulmonary artery pressure did not rise on exercise. When the mean pressure rose with increasing severity of the disease or after exercise, the pulse pressure widened (Figure II).

Oxygen Consumption

At rest the oxygen consumption for those who were regarded as basal averaged 117 cubic centimetres per square metre of body surface per minute, and there was no difference between the classes. This figure is of the same order as that obtained at catheterization for hospital female patients by Cournand *et alii* (1945) and for normal male subjects by Stead *et alii* (1945). The calculated metabolic rate is also in agreement with the basal figure obtained recently by Robertson (1952) for a very large series of normal controls. It is therefore unlikely that mitral stenosis, however severe, leads to any alteration in the basal metabolic rate. During exercise the oxygen consumption rose; whether the rise was normal for the amount of work done we are unable to say, as the work was not measured.

In plotting pressures and flows and in determining the statistical relationships between the classes, we have omitted patients with metabolic rates above +10% or pulse rates greater than 100 per minute. In all the latter patients the true resting pulse rate was known to be in the normal range for mitral stenosis.

Ventilation

In computing the means for the minute volume of respiration, it was thought legitimate to omit the few patients who were obviously hyperventilating. The mean of 3·4 litres per square metre of body surface per minute for Class II agrees exactly with that found by others (Stead *et alii*, 1945) for normal basal males, and is somewhat lower than that obtained by Cournand *et alii* (1945) for both normal males and hospital male and female patients under "standard" conditions. It is of some interest that there is an apparent slight increase in the mean ventilation in the third and fourth classes; but the figures are well within the range of normal observed by others, and on analysis of variance are not quite significant at the 5% level.

On exercise the ventilation has been related to the oxygen consumption and the three classes compared with the combined normal controls of Dexter *et alii* (1951) and Hickam and Cargill (1948). The mean slopes for the controls and the successive classes were 16·6, 29·8, 43·2 and 42·3 (Figure III). These figures are significant at the 1% level, and it can be assumed that as a class, patients who have mitral stenosis with symptoms ventilate excessively at very low levels of exercise.

Arterio-venous Oxygen Difference

Figure IV shows the change in the arterio-venous oxygen differences at rest and during exercise. The mean response for each class has been plotted, and the average normal response, calculated from the figures of Hickam

and Cargill (1948) and of Dexter *et alii* (1951), has been inserted on the graph. At rest the mean arterio-venous oxygen differences were 4·0, 4·9 and 6·4 volumes *per centum* for the three classes respectively, and the differences

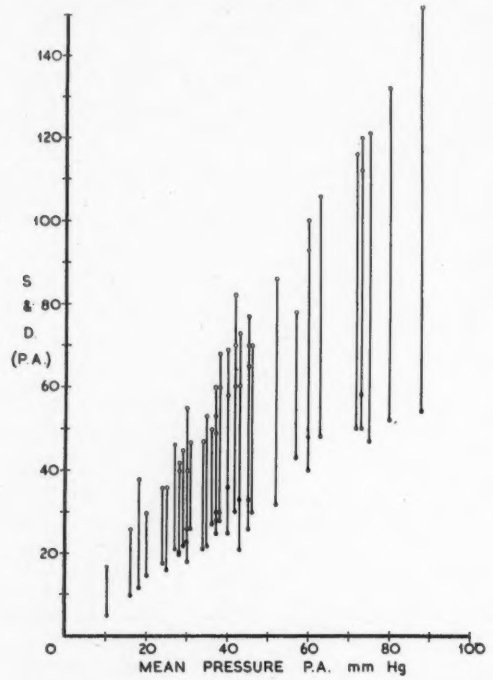

FIGURE II.

Pulmonary arterial systolic and diastolic pressures at rest plotted against mean pulmonary artery pressure. The two patients with the highest readings had definite pulmonary incompetence. The pulse pressure rises when mean pressure rises.

are significant. At rest all the observations in Class II, some in Class III and a few in Class IV were within the normal range. During light exercise some of the more mildly affected subjects in Class II responded normally, but the great majority showed an abnormal widening of the arterio-venous oxygen difference. The mean slopes of the classes differ between themselves and from the normal.

Cardiac Index

The means for the classes at rest were 2·9, 2·4 and 1·9 litres per square metre per minute. The differences are significant, and the general trend therefore is to a fall in cardiac output as the disease progresses. The great majority of the patients in Class II and some of those in Class III had resting cardiac indices which are in the low normal range (Stead *et alii*, 1945; Cournand *et alii*, 1945; Palmer and Walker, 1949). In Class IV the resting cardiac index was almost always low. On exercise every patient in Class II showed a rise in cardiac output, while in Class III 18 showed a rise, and the remainder no significant change.

In the fourth class a few had a significant rise and a few a significant fall, but the majority showed no change and though the mean for the group was slightly higher on exercise than at rest, the difference was not significant.

When the rise in the cardiac index with exercise was plotted against the rise in oxygen consumption per square metre of body surface (Figure V), it was at once apparent that the slopes of the lines in the different classes were different, and this was borne out by an analysis of variance. Furthermore, Class II, as a group, differed from the combined normal controls of

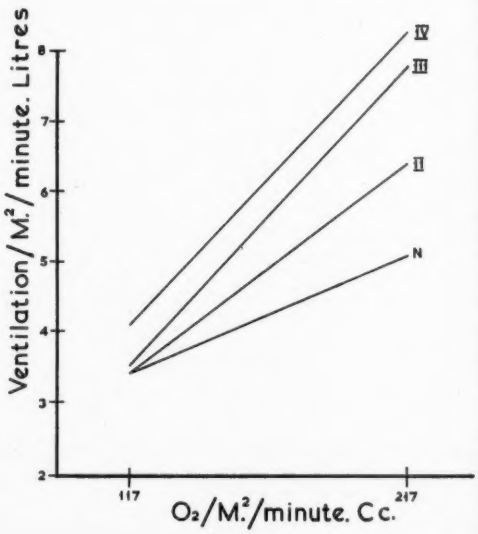

FIGURE III.

Mean values for ventilation and oxygen consumption at rest and during exercise. N, normal control series; and the figures refer to the classes discussed in the text.

Hickam and Cargill (1948) and of Dexter *et alii* (1951), and it can be concluded that as a group all our patients responded inadequately to exercise as far as the cardiac output was concerned. In some, it is true, the response was normal, but it is highly probable that at higher levels of exercise it would have been abnormal.

Pulse Rate

For those whose pulse rates were regarded as basal and whose rhythm was regular, the resting pulse rate of the whole series averaged 82 per minute, and the differences between the classes were not significant. Comparison with earlier work is difficult, as the majority of our patients were females who usually have a faster pulse than males. However, the mean happens to agree well with that found by Cournand *et alii* for their whole series of 34 subjects under "standard" conditions, and more significantly with their small series of six hospital female patients with normal circulation. On exercise (Figure VI) the pulse rate rose more in the third and fourth classes than in the second class, and the differences when related to standard oxygen consumption were highly significant. It was of interest that the rise in the fourth class was no greater than it was in the third. Whether the rise in Class II was abnormally great is not known, as there is no available normal series with comparable pulse rates at rest.

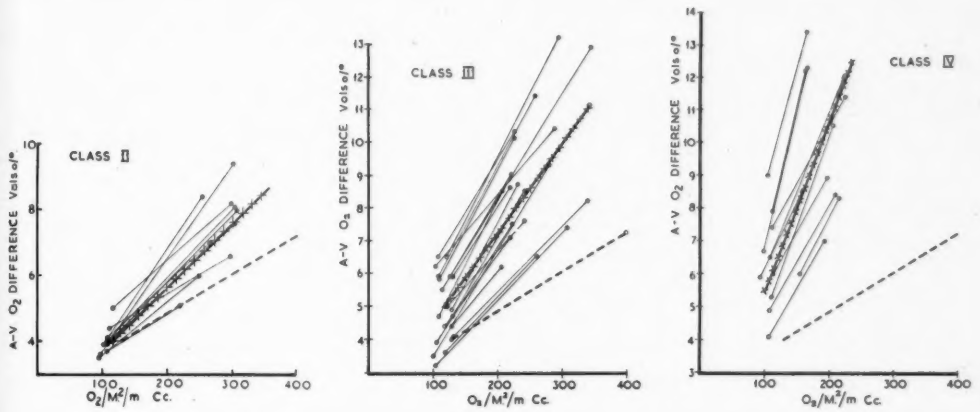

FIGURE IV.
Arterio-venous oxygen differences at rest and during exercise in Classes II, III and IV. Predicted mean normal response shown by interrupted line. Mean response of group shown by alternate crosses and lines.

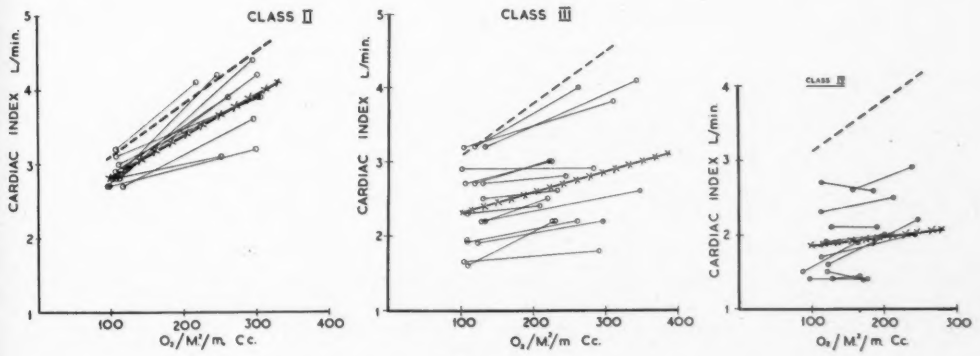

FIGURE V.
Cardiac index and oxygen consumption in the three classes. Means as for Figure IV.

Stroke Index

The stroke volume per square metre of body surface (stroke index) for the 11 basal subjects in Class II averaged 34 cubic centimetres per beat and the change on exercise was insignificant. As was mentioned previously, the resting pulse rate in this series was 83 per minute on the

average, as compared with a mean of 70 for 35 normal subjects (30 of them male) from the series of Cournand (1945) and Stead (1945). The average stroke index in that normal group was 47 cubic centimetres per beat, and even if allowance is made for sex, the difference in rate, and the slight alteration of diastolic filling period of the left ventricle, it is possible that a considerable number of our Class II patients had a diminished stroke volume at rest. In Classes III and IV the resting figures were even lower, and it was noteworthy that of 23 patients in

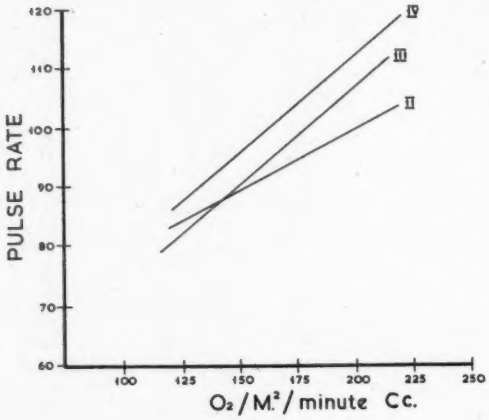

FIGURE VI.
Means for pulse rate at rest and during exercise in the three classes. The increase in Class II is significantly less than in Classes III and IV.

Class III, basal and otherwise, 19 had a fall of stroke index on exercise. In Class IV the stroke index was unchanged on exercise in three subjects and fell in the remainder.

Arterial Oxygen and Hæmoglobin Content

The arterial oxygen saturation was normal in all the patients of Class II, both at rest and during exercise. Of 23 patients in Class III, one (Case 15) had a slightly lowered saturation at rest and in three (Cases 18, 22 and 35) the arterial saturation was measured during exercise only and was found to be slightly low. In two of the latter pulmonary capillary pressures at the time exceeded 40 millimetres of mercury, while the third had obvious pulmonary œdema, but the capillary pressure was not measured.

In Class IV arterial unsaturation was present at rest in eight out of 16 patients. In one (Case 47) it was due to heavy sedation. In two, pulmonary œdema had been present recently or at the time of study, and in both of these pulmonary capillary pressure exceeded 30 millimetres of mercury. Of the remaining five, pulmonary capillary pressure was not known in one, and in four varied from 20 to 29 millimetres of mercury. "Capillary" pressures were of the same order in the patients with normal arterial oxygen saturation; moreover, one of these with the highest "capillary" pressure (Case 52) also had pulmonary œdema.

When the classes are surveyed together, it can be seen that there is a progressive increase in the frequency of arterial unsaturation as the disease progresses. In some cases in which it was found on exercise, it could perhaps be attributed to pulmonary œdema; but as was mentioned above, slight pulmonary œdema can occur with a normal arterial oxygen saturation. In other cases the finding of a greatly raised pulmonary arteriolar resistance immediately suggests the possibility of thickening of the alveolar blood gas barrier, with consequent impairment of diffusion. In Case 44 neither of these explanations seems adequate.

Recently Blount *et alii* (1952) have confirmed the lowered arterial oxygen tension in some cases of mitral stenosis, and have suggested that their results can be explained only by an increase in the very small amount of systemic venous blood which normally reaches the left ventricle (Donald *et alii*, 1952). Although it is known that communications between the bronchial and pulmonary vessels are abnormally dilated in mitral stenosis (Gilroy, Marchand and Wilson, 1952), the relative importance of venous admixture and alveolar diffusion difficulties in mitral stenosis has still to be determined.

Mitral Valve Area

In only three patients did the calculated valve area exceed 1·5 square centimetres. The differences between the means for the groups are highly significant and there is a good correlation between the severity of the symptoms and the size of the valve orifice.

Pulmonary Artery-Pulmonary "Capillary" Gradient

The pulmonary artery-pulmonary "capillary" gradient rose from Class II to Class IV. Six patients (Cases 1, 3, 4, 6, 7, 10) in Class II and three patients in Class III (Cases 17, 26 and 28) had gradients of less than 10 millimetres of mercury and were therefore normal in this respect. Seven of these nine patients had sinus rhythm with a normal cardiac output, and their valve areas were 1·2 square centimetres or more. The remaining two patients had auricular fibrillation with low cardiac outputs and valve areas of 0·9 square centimetre. In

the remaining 48 patients the gradient was raised. These results show that normal gradients are practically confined to patients with relatively high valve areas.

Pulmonary Arteriolar Resistance

The means for the classes show a progressive increase. If we assume an arbitrary upper normal limit of 150 dynes sec. cm.$^{-5}$, it will be seen that six patients (Cases 1, 3, 4, 6, 7 and 10) in Class II and one (Case 28) in Class III had normal resistances at rest. The remainder had raised arteriolar resistances, and in some patients in Class IV it was 10 to 15 times normal.

There is considerable room for error in the calculation of pulmonary arteriolar resistance during exercise, as it involves the measurement of three independent variables; this is particularly true if the state is not quite steady and pulmonary artery and pulmonary capillary pressures are not taken together. Moreover, a small error in the measurement of the gradient causes a large error in the calculation of the resistance. Nevertheless our results show no consistent change on exercise, the difference between the means in Class III proving on analysis to be without significance. The rise in Case 18 remains unexplained, and in spite of the slight arterial unsaturation on exercise is probably best attributed to undetected experimental error.

Total Pulmonary Resistance

The total pulmonary resistance depends on the resistance of the pulmonary arteriolar and capillary beds and the resistance of the stenosed mitral valve. If it is accepted that the pulmonary arteriolar resistance does not change during exercise and that the pressure rises in the left auricle, then it follows that the total pulmonary resistance must rise during exercise, and this was the case.

Elasticity Resistance (E)

If we assume a normal value for adults of 700 dynes cm.$^{-5}$ (Deucher and Knebel, 1952), it agrees well with the means of 740 and 792 for Classes II and III respectively. In Class IV with the exception of one patient (Case 45) the elasticity resistance was always above 1000 dynes cm.$^{-5}$, and in one basal patient without pulmonary incompetence a figure of 4945 was obtained. Tachycardia was with one exception consistently associated with marked rises in E; in the few patients in whom it has been measured during exercise, a similar rise occurred. In some patients with mild mitral lesions, and in others with auricular fibrillation, the elasticity resistance was low. In two patients with auricular fibrillation (Cases 40 and 45), both of whom had been in congestive failure, the elasticity resistance was within normal limits. It is apparent that down to a valve area of 0·9 square centimetre the great majority have an elasticity resistance at rest which is within the normal range or lower. In a few the rise, which in the absence of fibrillation is practically constant below this valve area, has made its appearance.

Right Auricular Pressure

Mean right auricular pressure has been preferred to right ventricular end diastolic pressure as an index of ventricular filling because of the ease of measurement and its proven reliability in this series. In the patients with sinus rhythm the means for the three classes were 0·5, 2·0 and 4·0 millimetres of mercury. For those with fibrillation the means in Classes III and IV were 3·0 and 9·0 millimetres of mercury respectively. There was therefore a rise in filling pressure as the disease advanced. The increases are small, but have added significance when one considers the narrowness of the normal range, and also that patients such as those in Cases 42, 44, 45 and 47 with filling pressures of five, two, three and six millimetres of mercury respectively were known to be close to congestive failure at the time of study. Resting pressures tended to be higher in patients with auricular fibrillation, though the numbers are too few to be conclusive.

On exercise right auricular pressure rose unmistakably in the four patients in Class IV in whom it was tested. In Classes II and III a slight but definite rise occurred in four of eight patients tested. In all eight patients the resting right auricular pressure was within the normal range of −2 to +2 millimetres of mercury (Bloomfield *et alii*, 1946).

Systemic Pressure and Resistance

Mean systemic blood pressure was within the normal range in all but three patients (Cases 11, 20 and 45), who had early essential hypertension. The peripheral resistance was therefore raised in those with low cardiac outputs. There was no consistent change on exercise. No attempt has been made to determine the regional changes in flow or resistance which these findings imply.

Work

Right ventricular pressure work varied from 0·4 kilogram metres per minute per square metre in Case 3, in which symptoms were

minimal, to 2·9 kilogram metres in Case 42, in which symptoms were present at rest. If we assume average normal mean pressures for pulmonary artery and right auricle as 10 and 0 millimetres of mercury respectively, and an average cardiac index of 3·4 litres per minute under basal conditions, then the mean value for right ventricular work at rest is in the vicinity of 0·5 kilogram metres per minute per square metre of body surface, and the upper limit of normal is probably less than 0·7 kilogram metre. Only three of the patients with sinus rhythm could be regarded as coming within the normal range.

As the valve area fell, right ventricular work increased in order to maintain the cardiac output. In most cases cardiac output at rest began to fall when right ventricular work was three or four times normal, but in Case 42 resting right ventricular work was about six times normal and the resting cardiac index was only slightly below normal. In patients with auricular fibrillation and in a few with sinus rhythm right ventricular work against pressure was considerably less than in the majority with sinus rhythm and comparable valve areas and filling pressures.

Discussion

The results show that with increasing severity of mitral stenosis the pressure in the pulmonary circulation and in the right side of the heart rises, while the flow initially maintained ultimately begins to fall. Because resting oxygen consumption and the calculated metabolic rate are unchanged, there is ultimately an abnormal widening of the arterio-venous oxygen difference, first on exercise and later at rest. Increasing resistance to flow in the pulmonary circulation leads first to diminished cardiac output, and finally to clinical congestive failure.

Ventilation and Dyspnœa

These observations show that a simple clinical appraisal of dyspnœa on effort gives a fairly reliable guide to the severity of the stenosis and the circulatory changes in the lungs. It is also probable that an objective method of measuring dyspnœa, such as that proposed by Hugh Jones (1952), would make this correspondence more exact, though the difficulties in applying such a method when the state of the lung changes so much on exercise are obvious.

At rest the total ventilation showed only a slight increase with increasing pulmonary congestion. On exercise there was an excessive increase of ventilation in proportion to the oxygen consumption even in Class II patients (Figure III). At very low levels of work the slope of the line relating ventilation to oxygen consumption was greater than it was for normal people doing five times as much work (data of Lindhard, quoted by Bock and Dill, 1931; Bock *et alii*, 1928). If at the same time the maximum breathing capacity is reduced, it follows that dyspnœa will be induced even more easily.

Finally it must be emphasized that these patients were exercised in the recumbent position. In the erect posture the increase in ventilation for a given amount of body work may well be much less.

Tachycardia

It has been noted by Meakins *et alii* (1923) and Ellis *et alii* (1951) and confirmed here

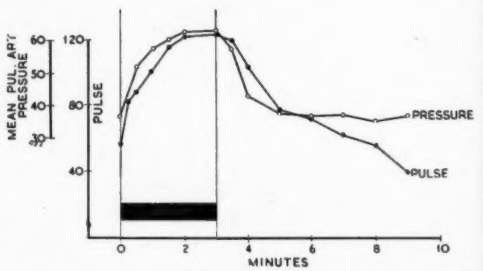

FIGURE VII.
Pulse rate and pulmonary artery pressure during exercise and recovery in Case 5.

that in mitral stenosis there is a disproportionate increase in heart rate with exercise. It is also apparent from our own data that in the absence of right ventricular failure, the pulse rate rises on exercise *pari passu* with the pulmonary artery and pulmonary capillary pressures (Figure VII). It is possible therefore that cardiac acceleration is related to pulmonary vascular distension; but whether this relationship is a direct one is not known.

Pulmonary Hypertension

The present findings confirm those of Borden *et alii* (1950) in showing a progressive increase in pulmonary artery pressure with increasing disability of the patient. However, there are occasional exceptions, particularly among the patients with auricular fibrillation, to which reference will be made later. The pulmonary artery pressure is the product of the pulmonary artery flow and the total pulmonary resistance. In mitral stenosis it depends on many factors, the most important of which are the competence

of the ventricles, particularly the right, the state of the arterioles, the size of the pulmonary capillary bed, the valve area and the rhythm. As long as the cardiac output at rest is normal, the mean pulmonary artery pressure gives a good measure of the severity of the disease.

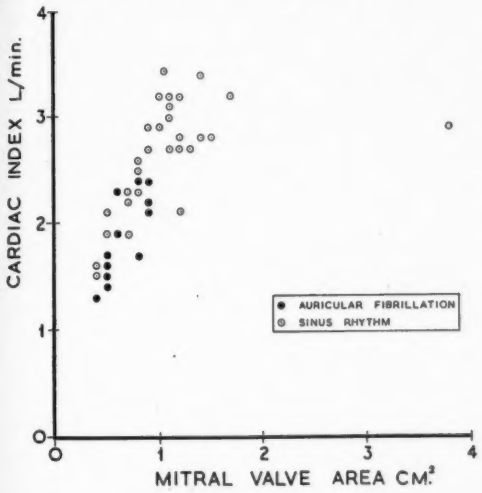

FIGURE VIII.

Cardiac index and mitral valve area. The normal mean basal cardiac index is probably in the range 2·9 to 3·1 litres per minute, a figure slightly lower than that originally obtained by Stead, Cournand and others. In this and succeeding figures illustrating the changes in cardiac output in the face of a diminishing valve area and a rising resistance, calculation of the true line has not been attempted, as the mathematical difficulties are considerable and their solution would be of little practical value. The precise valve area at which cardiac output begins to fall cannot be defined from the limited data available, but that such a point does exist for each patient and is not far removed from the suggested figures is reasonably certain.

When the cardiac output falls, the pulmonary artery pressure is no longer a direct indication of the total resistance to flow. Thus it is not surprising that the correlation between mean pulmonary artery pressure and the electrocardiographic signs of right ventricular hypertrophy is not precise (Trounce, 1952).

Nevertheless, in most cases a knowledge of the pulmonary artery mean pressure does give important evidence of the severity of the disease. This is so because in general the right ventricle reacts consistently to the increase in total resistance. Exceptions do occur from variation in the response of the ventricle, but they are few and can usually be recognized by other means.

Cardiac Output, Pulmonary Resistance and Auricular Fibrillation

This work and that of others (Carlotti *et alii*, 1952; Lewis *et alii*, 1952) shows that with a valve area of 1·5 square centimetres or more, cardiac output is normal at rest. No extra load is thrown on any cardiac chamber except the left auricle, in which a more vigorous systole may be needed to complete left ventricular filling. During exercise, however, left auricular, pulmonary and right ventricular pressures rise in order to maintain mitral valve flow. Exercise is probably limited by the elevation of pulmonary "capillary" pressure to levels which cause intense dyspnœa. With further narrowing of the valve, left auricular and pulmonary vascular pressures become abnormal at rest, and a rising pulmonary arteriolar resistance adds to the load on the right ventricle. Figure VIII shows that the cardiac index remains within the normal range until the calculated valve area is in the vicinity of one square centimetre or slightly less. Only one exception to this rule was found. Below the range 0·9 to 1·0 square centimetre, cardiac index and valve area fall together and the correlation between them is high.

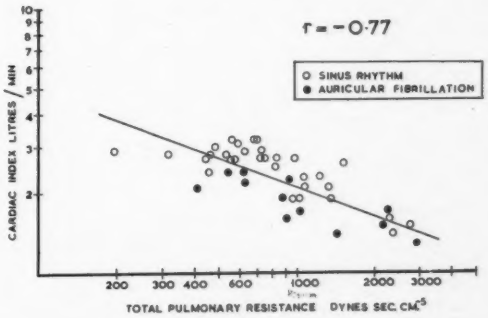

FIGURE IX.

Cardiac index and total pulmonary resistance (logarithmic). The straight line which fits the data best is expressed by the equation $y = -0{\cdot}35x + 0{\cdot}68$, but this is unlikely to be the true line.

In Figure IX cardiac index has been plotted logarithmically against total pulmonary resistance and the regression line calculated from the data. The correlation coefficient (r) is $-0{\cdot}77$, which is similar to the figure obtained by Gorlin, Haynes *et alii* (1951). A similar relationship holds for stroke index (Figure X). Gorlin, Haynes and others conclude, therefore, that in mitral stenosis cardiac and stroke index vary inversely as the total pulmonary resistance. However, it is unlikely that the straight lines of best fit adequately express the relationships. At low pulmonary resistances (and consequently high valve areas), which are poorly represented in our data, the lines lie somewhat above the expected normal levels for cardiac and stroke index under basal conditions. Patients with

auricular fibrillation fall as a rule below the line, particularly in the middle range of resistance.

In Figure XI data from eight patients with auricular fibrillation and two with sinus rhythm selected from the papers of Gorlin, Haynes *et alii* (1951) and of Lewis *et alii* (1952), and

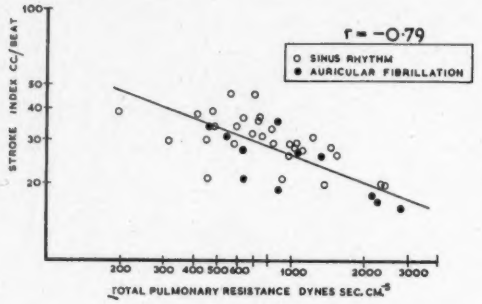

FIGURE X.
Stroke index and total pulmonary resistance (logarithmic);
$y = -0{\cdot}35x + 2{\cdot}48$.

with metabolic rates of the same order as those of our own patients, have been added to Figure IX. This shows more clearly that when sinus rhythm is present the cardiac index is maintained until the total resistance reaches the vicinity of 700 to 800 dynes sec. cm.$^{-5}$, which

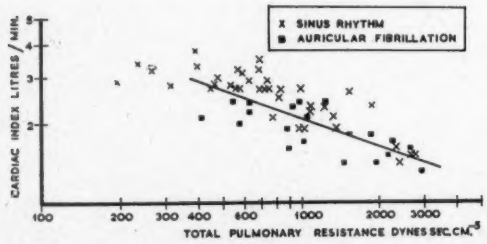

FIGURE XI.
Cardiac index and total pulmonary resistance (logarithmic).
For discussion see text.

corresponds to a valve area of 0·9 to 1·0 square centimetre. With a further increase in resistance the cardiac index falls progressively. The relationship between flow and resistance is therefore more complicated than at first appeared. When sinus rhythm is maintained considerable compensation for a raised resistance occurs, and until this approaches three or four times normal the cardiac output is maintained at rest. This compensation by the right ventricle in the face of pulmonary hypertension is comparable in degree to that achieved by the left in maintaining flow in systemic hypertension. Moreover, there is evidence that it is achieved in the same way—by cardiac hypertrophy and, in the later stages at least, by an increase in filling pressure. Auricular fibrillation is a serious complication, even when the rate is controlled by digitalis, for resting output falls and the response to exercise is less satisfactory.

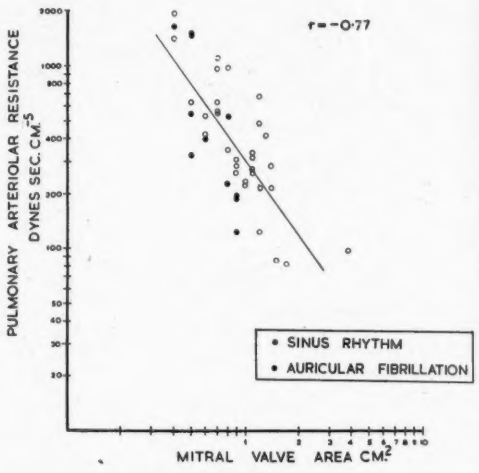

FIGURE XII.
Pulmonary arteriolar resistance and mitral valve area (logarithmic)
$y = -1{\cdot}33x + 2{\cdot}47$.

Figures XII and XIII demonstrate the close correlation between the mitral valve area and cardiac index on the one hand and pulmonary arteriolar resistance on the other.

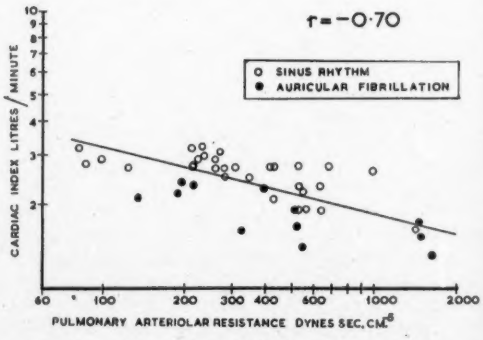

FIGURE XIII.
Cardiac index and pulmonary arteriolar resistance (logarithmic)
$y = -0{\cdot}24x + 0{\cdot}97$.

For patients of the mean age for this series (thirty-three years), the upper limit of normal for pulmonary arteriolar resistance is probably in the vicinity of 150 dynes sec. cm.$^{-5}$. In mitral stenosis an increase in resistance usually

begins in the stage of compensation, when the valve area is in the range 0·9 to 1·5 square centimetres, and rises abruptly to 10 or 15 times normal as the valve orifice shrinks to 0·4 square centimetre. For a given valve area, pulmonary arteriolar resistance and cardiac index are lower when auricular fibrillation is present.

In summary, it can be seen that mitral stenosis can be divided into three physiological stages, which are related to the area of the valve aperture. There is admittedly some overlap between the stages, but the distinction is sufficiently clear-cut to make it of value. In the first stage, pulmonary vascular pressures are within the normal range and cardiac output is normal at rest. The valve area lies between the normal of four to six square centimetres and 1·5 square centimetres. The response to exercise will be abnormal at variable work levels, depending on the size of the valve orifice. The load on the right side of the heart is abnormal only during exercise, and the lungs are normal at rest.

In the second stage the valve area lies between 0·9 and 1·5 square centimetres. Pulmonary vascular pressures at rest are raised, but the cardiac output is maintained. Obstructive changes have begun to appear in the lungs, and there is early congestion at rest. During exercise the pulmonary congestion increases owing to obstruction at the mitral orifice, and pulmonary vascular pressures rise. The cardiac output is inadequate for the work done, though it rises perceptibly.

In the third stage, in which the valve area is less than 0·9 square centimetre, cardiac output is inadequate at rest. Pulmonary vascular resistance increases greatly and may make the major contribution to the total resistance offered to the right ventricle. Pulmonary vascular pressures are higher at rest than in the second stage and rise even more on exercise, although the increase in flow is small or negligible.

Auricular fibrillation occurs with increasing frequency as the valve area falls below 1·5 square centimetres. Occurring early, it causes a fall in the cardiac output at rest, while if it occurs in the later stages of the disease its effect on the cardiac output is less noticeable.

Pulmonary Œdema and Pulmonary Arteriolar Resistance

It has been shown previously (Dexter *et alii*, 1950) and confirmed in this series that, as pulmonary " capillary " pressure at rest rises, a point is reached at which the pulmonary artery pressure rises disproportionately, so that the gradient increases with increasing severity of the disease. As the pulmonary " capillary " pressure approaches the 20 to 30 millimetres range, the rise in pulmonary artery pressure is precipitous. The osmotic pressure of the plasma proteins is of the same order as

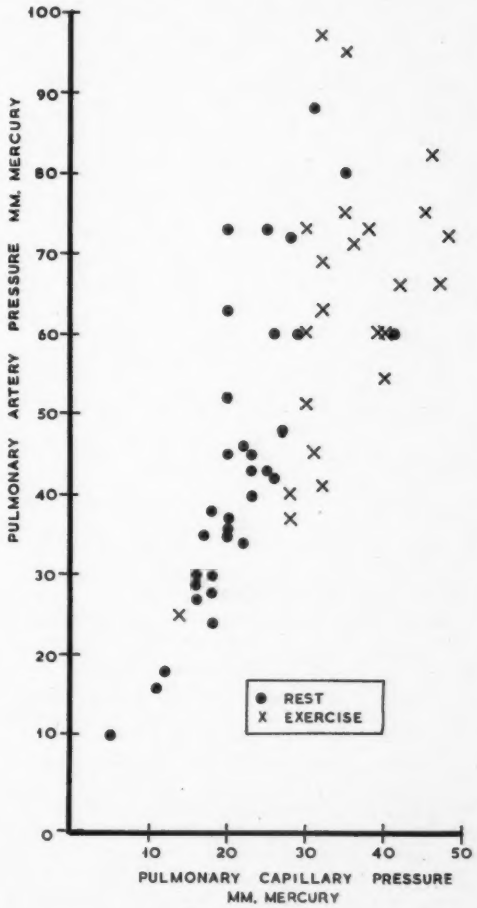

FIGURE XIV.
Pulmonary artery and pulmonary capillary pressure at rest and during exercise.

this critical pulmonary " capillary " pressure, and as has been shown by the data of Gorlin, Lewis *et alii* (1951) and ourselves, if this critical pressure is exceeded for more than a few minutes, pulmonary œdema will result ; this confirms in a general way for the lung the Starling hypothesis of fluid exchange in the tissues (Starling, 1909).

In Figure XIV pulmonary artery mean pressure is plotted against pulmonary "capillary" pressure at rest and on exercise. The correlation coefficient at rest for the straight line of best fit is 0·84, and for the true line it is probably higher. There were only three basal patients (Cases 42, 52 and 55) with a pulmonary "capillary" pressure at rest greater than 30 millimetres, and all three had had pulmonary œdema several times. Pulmonary œdema is more frequent at rest in the presence of tachycardia (Harken, Ellis, Ware and Norman, 1948) and a strong right ventricle.

When exercise is begun, there is an increase in venous return and in right ventricular output. Because of the smaller increase in valve flow, blood is trapped in the lungs and the "capillary" pressure rises. In the majority of the patients in this series œdema levels were reached, and in spite of the short duration of exercise, pulmonary œdema actually occurred in four (Cases 22, 29, 32 and 52). The pulmonary artery pressure also rose; but it is evident from the graph that it did not follow the line relating pulmonary arterial to pulmonary "capillary" pressure at rest. The gradient was smaller in spite of a larger flow. The resistance was therefore less.

It is at first sight a paradox that œdema levels of "capillary" pressure were reached on exercise in the laboratory in so many patients who had no history of spontaneous pulmonary œdema. On their being questioned, it was apparent that these patients had learned to regulate their activities by their dyspnœa. In those with a history of recent pulmonary œdema, pulmonary vascular resistance is usually lower and right ventricular performance better than in the average patient with a comparable valve area. In such patients the tachycardia of excitement or the increased venous return of exercise has, in our experience, brought on pulmonary œdema in a few minutes. We have found no evidence of reflex vasoconstriction in the lung except during severe anoxia. It seems unlikely that a rise in pulmonary "capillary" pressure *per se* would lead to vasoconstriction, for it is clearly ineffective in preventing pulmonary œdema, and in health it would be purposeless. However, if severe anoxia occurs as the result of pulmonary œdema, vasoconstriction almost certainly occurs. Our evidence on this point rests on two patients (Cases 38 and 47) with arterial saturation below 80% at the time of study. Their arteriolar resistances were 1359 and 1184 dynes sec. cm.$^{-5}$ respectively. In the first patient arterial anoxia was due to pulmonary œdema, in the second it was due to excessive premedication with morphine and hyoscine. In both, arterial saturation was normal next day. In neither patient did the other findings suggest such high arteriolar and total resistances. The first patient's heart was recatheterized six months after valvotomy and her arteriolar resistance found to be 345 dynes sec. cm.$^{-5}$. It is reasonable therefore to assume that at the time of first catheterization the resistances were high owing to anoxia.

Several recent papers confirm the earlier work of von Euler and Liljestrand (1946) in anæsthetized cats that anoxia causes a rise in pulmonary vascular resistance. Duke and Killick (1951) have shown that vasoconstriction occurs in the isolated perfused cat's lung and is thus independent of nervous control. In anæsthetized dogs Lewis and Gorlin (1952) and Peters and Roos (1952) have confirmed the original work, while in unanæsthetized dogs Stroud and Rahn (1952) found that breathing 8% oxygen mixtures caused a 100% increase in arteriolar resistance. In man, Motley *et alii* (1947) and Westcott *et alii* (1951) have found similar directional changes. Save for the two patients just discussed, it seems unlikely that such a reflex occurred either chronically or acutely in this series.

There is abundant evidence in animals that the pulmonary circulation can be influenced by nervous discharges (McDowall, 1938) and recent work (Gilmore and others, 1952) suggests that autonomic nerves may play a part in postural adaptation in man. Both noradrenaline and adrenaline constrict the pulmonary arterioles (Fowler, Westcott, Scott and Maguire, 1951; Witham and Fleming, 1951), while hexamethonium relaxes them. Despite these findings it is still true that "under variable physiologic conditions a clear-cut demonstration of vasomotor activity in the pulmonary vascular bed is still lacking" (Cournand, 1947).

It is therefore reasonable to relate the high arteriolar resistance found in so many cases of mitral stenosis to the structural changes described by Parker and Weiss (1936) and by Larrabee, Parker and Edwards (1949). The vascular thickening and occasional necrotic arteriolar changes closely resemble the changes seen in the systemic circulation in human and experimental renal hypertension. The necrotic lesions depend on the height of the blood pressure (Byrom and Dodson, 1948), and the endarteritic changes are probably due to the same cause (Moschkowitz, 1942). While organization of thrombi may contribute to

these changes in the lung there is no evidence at present to relate them chiefly to anything but the height of the pulmonary blood pressure. Thickening of the alveolar capillary barrier has no counterpart in systemic hypertension and is presumably due to organization of transudate resulting from temporary rises of " capillary " pressure above the osmotic pressure of the plasma proteins.

Elasticity Resistance

It is known that in mitral disease with pulmonary râles at rest due to pulmonary œdema, the distensibility of the lung is much reduced (Christie and Meakins, 1934). At this time the elasticity of the pulmonary vascular tree is also greatly reduced, and this must contribute to the rigidity of the lung as a whole. To our knowledge measurements of pulmonary distensibility have not been made in earlier stages of the disease; the present findings suggest that if it is abnormal at rest the abnormality cannot be attributed to vascular changes.

Recently it has been shown by Kopelman and Lee (1951) that pulmonary blood volume is normal at rest in all stages of mitral stenosis and rises only slightly on exercise. These workers attribute these findings to narrowing of the smaller vessels of the lung, which offsets the dilatation found in the larger vessels when the stenosis is severe and the cardiac output has begun to fall. Our findings suggest in addition that when pulmonary " capillary " pressure rises during exercise or tachycardia a much greater rise of the elasticity resistance occurs, so that small rises of volume cause a great rise in pressure. The pulmonary vascular tree becomes more nearly a rigid system, and any considerable volume increase is out of the question. This is true even of patients in whom the resting cardiac output is normal. The rise in elasticity resistance must also play a part in limiting stroke volume and cardiac output at rest and particularly during exercise, for it demands a rise in systolic pressure out of all proportion to the increase in flow.

Auricular Fibrillation

It has already been shown that when it occurs in the second stage or early in the third stage of mitral stenosis, auricular fibrillation leads to a fall in cardiac output of the order of 20% to 30%. This is in agreement with the findings of Smith, Walker and Alt (1930) and of Kerkhof (1936), who demonstrated a rise in cardiac output of the same order when fibrillation was converted to normal rhythm with quinidine. The present data also show that pulmonary arteriolar resistance and effective ventricular work against pressure tend to be lower and filling pressures somewhat higher when auricular fibrillation is present. It will also be shown in a companion paper that heart size is greater in the presence of fibrillation.

These findings may explain an earlier observation by Bayliss, Etheridge and Hyman (1950) that in some patients with severe disability the pulmonary artery pressure is nearly normal at rest but rises excessively with exercise; for if, as seems likely, the right ventricle is unable to compensate for the loss of left auricular systole, the flow will fall and vascular changes in the lungs will progress more slowly. Continued narrowing of the valve will further lessen flow and lead as in Cases 40, 45 and 48 to congestive failure with comparatively low pulmonary artery pressures. On slight exertion blood is trapped in the lungs and pulmonary pressures rise. At the same time right auricular pressure rises, giving ample evidence of failure. Occasionally similar changes are found in patients with sinus rhythm; this emphasizes the importance of the myocardium in maintaining flow in the face of a rising resistance.

The fall in cardiac output with the onset of fibrillation must, in the final analysis, depend on inadequate performance of the right ventricle, which is unable to compensate for the loss of left auricular systole. The contribution of the auricular systolic fraction to left ventricular filling has not yet been measured in man. In both normal dogs (Wiggers, 1923) and dogs with acute mitral stenosis (Katz and Siegel, 1931), this contribution appears to be considerable. At the same time it is possible that after the occurrence of acute mitral stenosis in dogs there may be a compensatory rise in right auricular pressure (Opdyke and Brecher, 1951). Provided there is a measurable gradient across the mitral valve, the auricular systolic fraction should be measurable from left auricular and left ventricular pressure tracings taken at operation. In a preliminary analysis of left auricular pressure tracings our results have been variable. Meanwhile it seems unjustifiable to attribute the fall in output we have found entirely to the lack of left auricular systole. It is perhaps significant that auricular fibrillation usually appears first in mitral stenosis, when the load on the right ventricle is considerable and filling pressure has probably already begun to rise.

Operative Treatment

Although the results of mitral valvotomy and its effect on the dynamics of the circulation

will be the subject of a later paper, certain conclusions which follow logically on the work presented here can be drawn. When mitral valvotomy was first introduced it was natural for physicians to select for surgery those patients who were in the terminal stage of the disease. Quite apart from the surgical difficulties due to large left auricles, thrombus formation and calcification of the valve, it is now clear that such patients usually had advanced changes in the pulmonary vessels and evidence of ventricular failure. If the surgeon's splitting of the commissures is going to be permanent—and there is evidence that this will be the case for many years at least—then it would seem rational to advise surgical treatment before the cardiac output has fallen and before changes have occurred in the lungs. This would correspond to the stage of dyspnœa on slight exertion when the valve area is approaching one square centimetre.

Summary and Conclusions

1. Fifty-seven patients with mitral stenosis have been studied by cardiac catheterization. The great majority were in or near the basal state at the time of study. The patients had been placed on clinical grounds in the functional classes of the New York Heart Association.

2. In the resting subject, as one passed from Class II to Class IV, the following changes in the dynamics of the circulation were found: (i) a decrease in valve area; (ii) a rise in the arterio-venous oxygen difference and a fall in cardiac output and stroke volume—the oxygen consumption was unchanged; (iii) a rise in pulmonary vascular pressures; (iv) a rise in right auricular pressure.

3. During exercise pulmonary vascular pressures rose out of all proportion to the increase in cardiac output, which was determined chiefly by the laws governing mitral valve flow. The pulse rate rose excessively and the stroke volume tended to fall. In Class IV incompetence of the right ventricle comes to dominate the picture, and the cardiac output, low at rest, did not rise significantly with exercise, although pulmonary artery pressure rose precipitously; right auricular pressure also rose on exercise.

4. On the whole there was a good correlation between the disability of the patient and the changes in the pulmonary circulation.

5. On analysis of the data it became clear that patients with mitral stenosis fit into three fairly well-defined hæmodynamic stages. (i) In the first stage the valve area is between the normal of four to six square centimetres and 1·5 square centimetres. Pulmonary vascular pressures and cardiac output are within the normal range at rest; both rise on exercise to a degree determined largely by the severity of the stenosis. During light exercise the rise in cardiac output is within normal limits; during heavy exercise it is probably abnormal. During this stage the resting load on the right ventricle is not abnormal, and hæmodynamic changes are probably confined to the left auricle. (ii) In the second stage the valve area is between 1·5 and 0·9 square centimetres. Pulmonary vascular pressures are raised at rest and rise even more on exercise. The cardiac output is maintained at rest by various compensatory mechanisms, the chief of which are probably right ventricular hypertrophy and a slightly raised filling pressure. During light exercise the cardiac output rises less than normally, and in some patients there is also a rise in filling pressure. It is during this second stage that rises in the pulmonary vascular resistance begin to appear. (iii) In the third stage the valve area is less than 0·9 square centimetre. Pulmonary vascular pressures are usually four times normal or even more, and the cardiac output at rest is low. The filling pressure has risen in the majority of these patients. During exercise pulmonary vascular pressures and filling pressures rise, but the increase in cardiac output is negligible. In most patients pulmonary vascular resistance rises greatly, though there are exceptions. In these latter patients, right ventricular incompetence has presumably appeared earlier and has lessened pulmonary vascular pressures.

6. Auricular fibrillation is not found usually before the second stage. Occurring early, it causes a fall in cardiac output of 20% to 30%. Pulmonary vascular pressures fall and pulmonary vascular thickening (*vide infra*) progresses less rapidly. It is probable that the filling pressure rises. If fibrillation occurs late, the effect on the cardiac output is less noticeable.

7. A small number of patients with sinus rhythm resemble those with auricular fibrillation, in that cardiac output is lower than the valve area or the vascular resistance would suggest. Taken as a whole the response of the output to an increasing resistance in patients with sinus rhythm is not linear, as the output is maintained until total resistance reaches three or four times normal.

8. No evidence of pulmonary vasomotor activity was obtained in these studies at rest or during exercise. However, in two patients

reduction of arterial oxygen saturation to less than 80% appeared to cause pulmonary arteriolar constriction. The view is therefore advanced that the raised arteriolar resistance seen in the later stages of the disease is structural in origin, though not of necessity entirely irreversible. Shrinking of the valve orifice and an increase in vascular resistance are believed to cause right ventricular failure.

9. The elasticity resistance, with some exceptions, was normal or even low until the third stage of the disease was reached. It rose acutely when pulmonary pressures rose during exercise or tachycardia.

10. Such a study as this cannot give information about many factors which must influence physicians and surgeons in choosing the optimal time for mitral valvotomy; but as a result of this work it would appear advisable to recommend this operation before the cardiac output has fallen and organic changes have appeared in the pulmonary circulation. This would correspond symptomatically to the stage of dyspnœa on light exertion.

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STUDIES IN MITRAL STENOSIS[1]

II. THE ELECTROCARDIOGRAPHIC AND RÖNTGENOLOGICAL FINDINGS

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In the preceding paper we have presented the results obtained by cardiac catheterization in 57 cases of mitral stenosis. It is the object of this paper to determine to what extent the electrocardiographic and röntgenological findings reflect the physiological observations in the same 57 cases.

Clinical Material

The 57 patients were considered to be suffering from predominant mitral stenosis. The criteria used to establish this diagnosis have been enumerated in the preceding paper. In addition, tricuspid stenosis has been excluded by a comparison of the right auricular and right ventricular end-diastolic pressures at cardiac catheterization, which has also helped to exclude any case of left to right intracardiac shunt, especially auricular septal defect.

The cases have been divided into three groups labelled Class II, Class III, Class IV according to functional capacity. For convenience these classes have been defined in the previous paper, and cases within each of these groups have the same numbers as in the preceding paper.

Full clinical details will be given in the final paper of this series.

Methods

Electrocardiography was employed as follows: Standard, unipolar limb and six precordial leads (*V*1 to *V*6) have been recorded. Strict attention has been paid to standardization (1 mv. = 1 c.m.) and to accurate electrode positioning.

To establish standards for this study, the electrocardiograms of 50 normal subjects ranging in age from fifteen to sixty-five years have also been analysed. These patients were known to have no organic heart disease, and the electrocardiogram was taken in most instances as part of a routine physical examination.

Teleröntgenograms were taken at a tube distance of six feet from the film; postero-anterior, right and left anterior oblique views with and without a barium bolus were recorded. Fluoroscopic examination was carried out in all cases, usually with several of the authors present.

Results

The Electrocardiogram

The effects of mitral stenosis on the electrocardiogram have been known for many years (Lewis, 1913; White and Burwell, 1924; Alexander, Knight and White, 1925). The work of these authors was a natural sequence to the association of the *P* wave of the electrocardiogram with auricular activity (Einthoven, 1906, 1908; Kraus and Nicolai, 1907; Samojloff, 1909). Since then, abnormal *P* waves, "exaggerated in amplitude, often broad, flattened or notched" (Lewis), right axis deviation, right ventricular preponderance and a high incidence of auricular fibrillation, have been accepted as of frequent occurrence in mitral stenosis. Berliner and Master (1938) have correlated the autopsy and electrocardiographic findings in cases of mitral stenosis with and without other valvular lesions, and recently White, Parker and Master (1944) and Rasmussen (1948) have published further extensive reviews. With the advent of cardiac catheterization, further knowledge of the lesser circulation has become available, and Lewis *et alii* (1952) and Trounce (1952) have used this additional information for a more complete analysis of the electrocardiographic findings in cases of chronic rheumatic mitral valve disease.

P Waves

Among the 57 patients, there were 12 with established auricular fibrillation, one with auricular flutter, and 44 with sinus rhythm.

Height of P Waves. The average height and range of *P*1, *P*2 and *PV*1 in 50 normal controls

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TABLE I.[1]

The Height of P Waves in Normal Controls and in 44 Patients with Mitral Stenosis. (Mean Values)

Wave.	Normal Controls.		Patients with Mitral Stenosis.					
			Present Series.				Berliner and Master.	
	Present Series.	White (1944).	Class II.	Class III.	Class IV.	Mean.	Mitral Stenosis.	Mitral and Tricuspid Stenosis.
*P*1	0·77	0·68	1·30 (1·00–2·00)	1·50 (1·00–2·00)	1·50 (1·30–2·50)	1·43	1·25	1·62
*P*2	1·10	1·56	1·59 (1·0–3·0)	1·84 (1·0–3·0)	2·80 (2·0–4·5)	2·08	1·63	2·62
*PV*1	0·37	—	0·60 (0–1·00)	0·80 (0–1·00)	1·30 (0–2·0)	0·90	—	—

[1] Measurements in millimetres.

and in the 44 patients of this series are shown in Table I. The frequency distribution of the height of *P*2 in the patients with mitral stenosis is shown in Table II. The values of the control

TABLE II

*Frequency Distribution of Height of P*2.

Height *P*2. (Millimetres.)	Class II.	Class III.	Class IV.	Total.	Percentage of Total.
0 to 0·5 ..	0	0	0	0	0
0·5 to 1·0 ..	4	2	0	6	14·0
1·0 to 1·5 ..	5	6	0	11	25·0
1·5 to 2·0 ..	4	7	3	14	32·0
2·0 to 2·5 ..	0	1	4	5	11·0
2·5 to 3·0 ..	1	2	2	5	12·0
3·0 to 3·5 ..	0	0	1	1	2·0
3·5 to 4·0 ..	0	0	1	1	2·0
4·0 to 4·5 ..	0	0	1	1	2·0
Total ..	14	18	12	44	100·0

group agree with those of most authors. Ashman and Hull (1941) have stated the normal range of *P*1 to be 0 to 1·10 millimetres and of *P*2 0·30 to 2·50 millimetres. White, Parker and Master (1944) obtained a mean value for the height of *P*2 of 1.56 millimetres, which is somewhat in excess of our findings. The results in the present cases of mitral stenosis show that the *P* wave is of greatest height in lead II, and the greatest increase in height occurred between Class III and Class IV (1·84 to 2·80 millimetres). Berliner and Master found the average height of the tallest *P* wave in each case of their series to be 1·63 millimetres. They anticipated that *P* waves of 2·5 millimetres or more would be found only when there was hypertrophy of both atria. The significance of this statement will be discussed in a later section.

White, Parker and Master (1944) constructed frequency distribution curves for the height and duration of *P* waves in normal controls, and in patients with mitral stenosis and mitral insufficiency, from which it is possible to anticipate the percentage number of cases in an unselected group of mitral stenosis, in which the height and duration of *P*2 will be of any particular value. Table III shows the frequency distribution of the amplitude of *P*2 in our cases, together with the predicted frequency with which *P* waves of a known height may be expected in an unselected group. There is reasonable agreement between these predicted values and the frequencies existing in the present 44 cases, despite the preselection previously mentioned. It will be seen that in approximately 20% of all cases of mitral stenosis it can be expected that *P*2 will be greater than three millimetres in height. Such cases are practically limited to Class IV.

TABLE III.

*Predicted and Actual Frequency of Height of P*2 *in Mitral Stenosis*

Height of *P*2. (Millimetres.)	Number of Cases.	Predicted Frequency Percentage.	
		Present Authors.	White.
1·0 and over	44	100	70
1·5 and over	38	86	68
2·0 and over	24	54	52
2·5 and over	11	25	38
3·0 and over	8	19	22
3·5 and over	2	5	11
4·0 and over	1	3	6
4·5 and over	0	0	0

Duration of P Waves. Tables IV and V show the mean values, range and frequency distribution of the duration of *P*2 and *PV*1. In the cases of mitral stenosis there is a progressive lengthening of the duration of *P*2 from

TABLE IV.[1]

Duration of P2 and PV1 in Normal Controls and in 44 Patients with Mitral Stenosis. (Mean Values)

Wave.	Normal Controls.		Mitral Stenosis: Present Series.				White (1944).
	Present Series.	White (1944).	Class II.	Class III.	Class IV.	Mean.	
P2	0·090 (0·07–0·12)	0·093	0·118 (0·08–0·15)	0·128 (0·10–0·16)	0·140 (0·13–0·15)	0·129	0·106[2]
PV1	0·090 (0·06–0·12)	—	0·120 (0·08–0·15)	0·126 (0·10–0·17)	0·141 (0·12–0·16)	0·129	—

[1] Duration in seconds.
[2] Widest *P* wave in any lead.

Class II to Class IV, but the percentage increase in duration is less than for the height of *P2*. These findings suggest that, as the functional capacity of patients decreases from Class II to Class IV, *P* wave changes, in height more than duration, are likely to be present.

as being either broad, flattened or notched, the changes being seen most frequently in lead 1 or 2 or in the left precordial chest leads. Of the 44 cases, in five (Cases 2, 4, 5, 10 and 21), normal *P* waves were present (Figure IA), and in 27 there was a bifid or broad wave—the

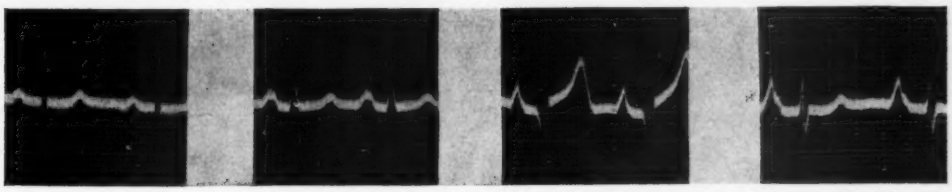


FIGURE I.

Varieties of *P* waves seen in normal subjects and in patients with moderate and severe mitral stenosis and severe pulmonary stenosis.

TABLE V.

Frequency Distribution Duration of P2.

Seconds.	Class II.	Class III.	Class IV.	Total.	Percentage of Total.
0·08	1	0	0	1	2·0
0·09	1	0	0	1	2·0
0·10	1	1	0	2	5·0
0·11	0	1	0	1	2·0
0·12	7	4	1	12	27·0
0·13	1	2	1	4	9·0
0·14	1	8	3	12	30·0
0·15	2	2	6	10	21·0
0·16	0	0	1	1	2·0
Total ..	14	18	12	44	100·0

P-R Interval. The *P-R* interval in Classes II, III and IV was 0·18 (0·16 to 0·24), 0·17 (0·14 to 0·22) and 0·21 (0·18 to 0·24) second respectively. In the control group it was 0·17 (0·13 to 0·20) second. Class IV only showed a significant difference from normal.

Contour of P Wave. The contour of the *P* wave in mitral stenosis is commonly described "*P* mitrale" of Winternitz (1935) (Figure IB). In the remaining 12 cases there was a broad tented *P* wave (Figure ID). A recent report by Wenger and Hofmann-Credner (1952) has shown that this bifid *P* wave is composed of both right and left auricular components, the initial peak being right auricular in origin. This was demonstrated by recording simultaneously right precordial (*V1*), intraauricular, and œsophageal leads—the œsophageal lead when correctly placed recording predominantly left auricular activity (Luisada, 1940). In 36 of the present 44 cases *PV1* has been biphasic, the change from positivity to negativity suggesting a resemblance to the intrinsicoid deflection of the *P* complex recorded by an intracardiac lead (Levine *et alii*, 1949; Kossmann *et alii*, 1950; Hecht and Woodbury, 1950). Tracings taken in this laboratory with intraauricular leads have shown that the intrinsicoid deflection of the *P* wave occurs almost simultaneously with the positive deflection of the biphasic *P* wave in right-sided precordial leads. It would therefore appear that the *P* wave in lead *V1*

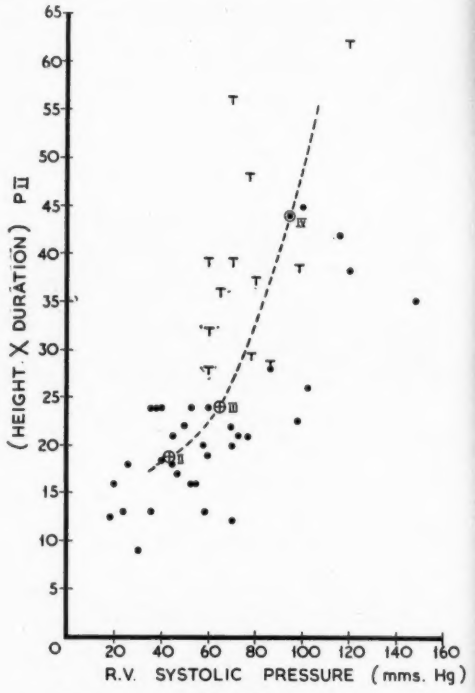
reflects very largely, because of its proximity to the right auricle, the electrical activity of this chamber. In all cases of mitral stenosis in which the *P* waves were notably bifid in either the standard limb or the left-sided precordial leads (*V*3 to *V*6), the time interval between the first peak of such a wave and the beginning of the succeeding *QRS* complex equalled the interval between the peak of the positive deflection in *PV*1 and the *QRS* complex in *V*1.

These observations are further confirmation of the views of Wenger and Hoffman-Credner that the bifid *P* wave so characteristic of mild and moderate mitral stenosis is composed of two positive elements—the first contributed by right auricular and the second by left auricular activity.

Berliner and Master (1944) observed that the greatest degree of increase in the amplitude and duration of the *P* wave, together with peaking or tenting of its contour, was found only in hearts with hypertrophy of both atria and therefore seen most frequently in cases in which tricuspid stenosis was also present. More recently, Trounce (1952) has also observed these tented *P* waves in 11% of his series of cases of mitral stenosis. Of the present series, in 12 out of 44 (27%) broad, high and peaked *P* waves have been present. These resembled those usually designated *P* "*pulmonale*" (Winternitz, 1935), differing, however, in the important feature that the duration has been greater than 0·12 second. The characteristics of the "pulmonary" *P* wave (Figure Ic) have been stated by Scheleser and Langendorf (1942) to be as follows: (i) The duration of the *P* wave in any lead is not greater than 0·12 second. (ii) The height of *P*2 and *P*3 is greater than the height of *P*1, which should never exceed 1·5 millimetres.

The exact significance of the "pulmonary" *P* wave has been greatly debated. Kahn (1927) and Winternitz (1935) originally suggested that it represented "the effect of pulmonary stasis on the right heart", or "strain on the right auricle". Wood (1948) was unable to find such a *P* wave in 100 normal control electrocardiograms, and stated that it was never seen in a normal vertical heart. Goldberger and Schwartz (1946) have stated that tenting of the *P* wave, seen most frequently in chronic pulmonary and congenital heart disease, is due to a clockwise rotation of the heart around its long axis combined with forward rotation of the apex. Hecht (1937), Fox and Kremer (1943), Scheleser and Langendorf (1942), and recently Zollner (1949) have found such a combination in electrocardiograms where the heart occupied an intermediate or vertical position. These authors do not consider that such a change in the *P* wave is related to right auricular hypertrophy. There is therefore no unanimity of opinion as to whether these *P* waves are the result of abnormal cardiac rotation or are an expression of right auricular hypertrophy. The findings of Berliner and Master suggest the latter explanation.

It was observed that the summit of the broad, tented *P* waves in the present series



GRAPH I.

Comparison of (height × duration) *P*2 with right ventricular systolic pressure. The mean values for each functional class are shown. *T* represents cases showing tented *P* waves.

occurred at such an interval prior to the succeeding ventricular complex as to suggest that the right auricle was contributing largely to their formation. This conclusion was reached because the interval between the summit of the *P* wave and the succeeding *QRS* complex was identical in both *V*1 and leads (usually 2, 3, *aVF*) demonstrating the tented appearance. As these tented *P* waves occurred almost exclusively in functional Class IV, in which the greatest degree of pulmonary hypertension and cardiac enlargement occurred, it seemed justifiable to conclude that they were in some manner

related to this increased pressure in the pulmonary circulation. It is our impression, therefore, that, in the natural history of mitral stenosis, as right ventricular hypertrophy increases, the right auricular element of the *P* wave comes to predominate, producing a peaked *P* wave of the type frequently found in tricuspid stenosis, which may therefore conveniently be termed a "tricuspid" *P* wave (Figure ID). This wave may be defined as a tall, pointed and broad *P* wave, greater than 2·5 millimetres in height and 0·12 second or more in duration.

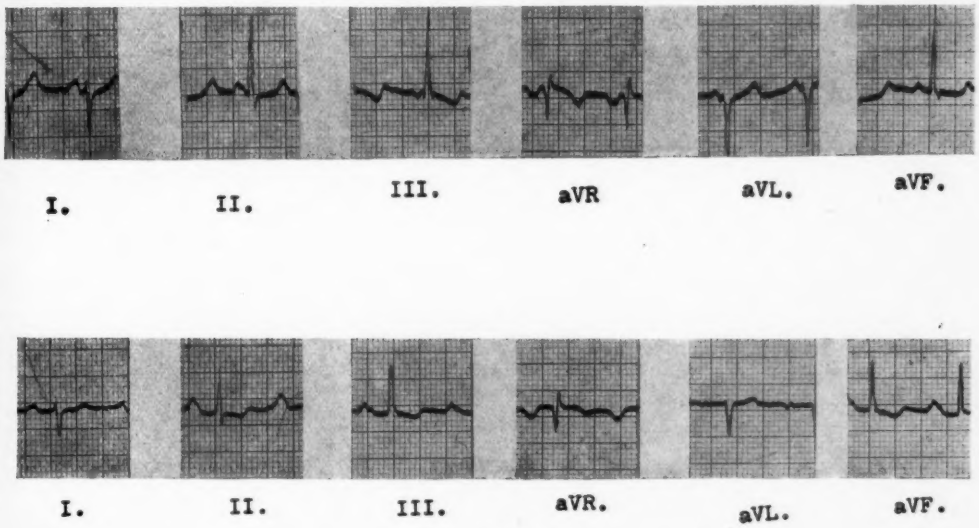


FIGURE II.
Distribution of abnormal *P* waves in mitral stenosis. Top tracing shows abnormal P_1, P_2, lower tracing abnormal P_2, P_3, *PaVF* distribution.

Graph I has been prepared by plotting the product of the height and duration of P_2 against right ventricular systolic pressure. The cases in which "tricuspid" *P* waves were present have been marked with a "*T*". Such points approximate the upper limits of a curve joining the mean values for each class. From this graph it would appear that the electrical activity of the right auricle and right ventricular systolic pressure are, in some manner, interrelated. No correlation existed between the area of P_2 (height $P_2 \times$ duration P_2) and mean right auricular pressure, although peaked *P* waves were in general associated with high mean right auricular pressure. Further work is in progress in an attempt to establish a relationship between the area of P_2 and right auricular systolic pressure, as it seems from preliminary studies that this factor would be more related to the area underlying the *P* wave than right auricular mean pressure.

Equally striking as the change in contour of the *P* waves has been the tendency for the abnormal *P* waves to be grouped in either leads 1 and 2 or leads 2, 3 and *aVF* (Figure II). The P_2 P_3 *PaVF* grouping occurred in nine out of twelve cases in Class IV. It seems that the more severe the clinical manifestations become, the more likely are the *P* waves to become higher, and to assume a tented appearance, and for these changes to be reflected in leads 2, 3 and *aVF*. It is apparent that when the mean *P* wave vector is increasingly directed towards the left leg the voltage of P_3 will become greater. The reason for such a change in the direction of the mean *P* wave vector could be due to cardiac rotation, to auricular hypertrophy, or to a combination of both factors.

The Ventricular Complex

When changes occur in the ventricular complex they are those associated with right ventricular hypertrophy.

For the purpose of this study the following criteria of right ventricular hypertrophy have been used (Mounsey 1952). (i) Prolongation of the time interval between the beginning of the *QRS* complex and the onset of the intrinsicoid deflection in V_1, usually greater than 0·03 second. (ii) A total duration of *QRS* complex less than 0·12 second. (iii) A tendency to a

small *Q* wave in *V*1. (iv) A reversal of the ratio of amplitudes of the *R* and *S* waves in *V*1, *V*6 characterized by an abnormally large *R* in proportion to *S* in *V*1 and prominent *S* in *V*6. (v) Inversion of *T* in *V*1, this inversion at times extending in varying degree as far as *V*4, but with an upright *T* wave in *V*6. (vi) Absence of notching of *R* in *V*1 except where it is preceded by a *Q* wave. It was apparent early in this analysis that the form of

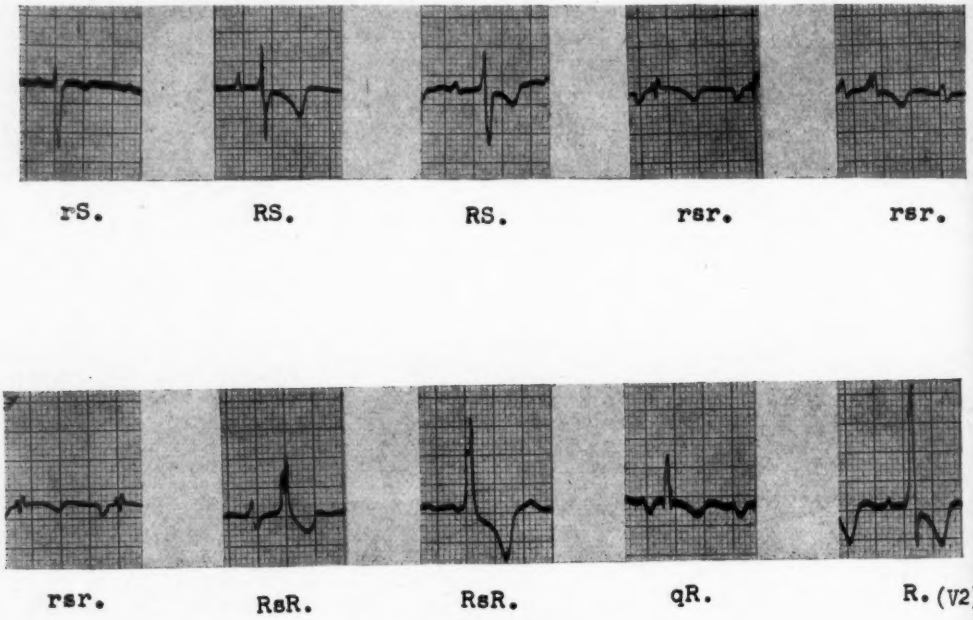


FIGURE III.
Varieties of *QRS* complex seen in *V*1.

the *QRS* complexes in *V*1 was readily divisible into three main groups as follows: (*a*) *rS*, *RS* or *Rs* complexes, the main feature being a ventricular complex in which an easily visible *S* wave was still present; (*b*) "*RSR*" complexes—characterized by the absence of an initial *q* wave, often multiple splintering of the *R* and *S* waves, with the total duration of the *QRS* complex of less than 0·12 second; (*c*) *R* or *qR* complex with no *S* wave present, the duration of *QRS* being less than 0·12 second (Figure III).

The percentage distributions of these three patterns for the whole series were 34, 39 and 27. Table VI shows that the frequency of these combinations corresponded closely according with the functional classes II, III, IV—the *rS*, *RS* or *Rs* pattern occurring in 79% of cases of Class II; an "*RSR*" combination in 56% of Class III and an *R* or *qR* pattern in 65% of Class IV. It was felt that it would be of more value to relate these patterns to evidence of right ventricular hypertrophy than to adhere to an analysis of all tracings within each functional class.

The rs, RS and Rs Group. Table VII shows normal values for *R*, *S*, *R*/*S* ratio in lead *V*1, compared with similar values of the *rS* and

TABLE VI.
*Frequency Distribution of QRS Patterns in V*1.

Class.	*rS.*	*RS.*	*Rs.*	"*RSR.*"	*qR.*	Total.
Class II	10	1	0	3	0	14
Class III	3	2	2	14	4	25
Class IV	0	1	0	5	11	17
Total	13	4	2	22	15	56

(*RS* and *Rs*) groups of patients with mitral stenosis. Although the mean value of *SV*1 is reduced in the *rS* group of mitral stenotics, the mean value of the *R*/*S* ratio remains the same as for normals. The mean value of the *R*/*S* ratio for the combined *RS* and *Rs* group is increased and is greater than unity, a value

TABLE VII.[1]

Measurement of R, S and R/S Ratio in Lead V1 in Normals and in 56 Subjects with Mitral Stenosis. (Mean Values)

Lead V1.	Normal Subjects.					Mitral Stenosis.	
	Thomas (1948).	Leatham (1950).	Goodwin (1952).	Present Writers (1953).	Mean.	*rS.*	*RS+Rs.*
R	4·4	2·9	5·0	1·8	3·5	2·2	6·4
S	12·0	10·0	10·0	10·2	10·5	7·0	4·8
R/S	0·37	0·29	0·50	0·17	0·33	0·32	1·34

[1] Measurements in millimetres.

which is accepted to indicate right ventricular hypertrophy.

The "RSR" and R, qR Groups. Owing to the variation of the deflections of the "*RSR*" group (*rsr*, *rSr*, *rsR*, *RSR* complexes all being seen, Figure III) and to the low voltages of many of the deflections, it was difficult to measure the relative heights of *R* and *S* waves with accuracy. The ratios of *R/S*, *V*5, *V*6 were, however, measured and will be discussed below. In the *R*, *qR* group, the *RV*1 had a mean height of 8·7 millimetres, with a range of 4·5 to 17 millimetres. In all instances in which an "*RSR*", *qR* or *R* configuration was present, the duration of *QRS* was equal to or greater than 0·08 second, but never more than 0·12 second. The intrinsicoid deflection measured from the beginning of the *QRS* complex to the peak of the tallest *R* wave exceeded 0·03 second. No example of complete right bundle branch block was encountered.

*Height of R, S and R/S Ratio in V*5 *and V*6. Table VIII shows the above values in the main electrocardiographic groups. There is a progressive diminution in the *R/S* ratio as one passes from the *rS* to *R*, *qR* groups defined above. This is caused mainly by an increasing depth of the *S* wave in left precordial leads.

Tall Secondary R Wave in aVR. Schack, Rosenman and Katz (1950) and Kilpatrick (1951) have drawn attention to this sign as confirmatory evidence of right ventricular hypertrophy. The secondary *R* wave in *aVR* has been regarded as significant where its height exceeded by one-half the depth of the previous negative deflection. Such a sign was positive in four (21%), nine (41%) and nine (60%) of the patients in the three electrocardiographic groups. In the control series only two (4%) of the tracings showed a similar change.

T Wave Inversion in Precordial Leads. Inversion of the *T* wave in lead *V*1 occurred in 19% of a normal series (Leatham, 1950) and in 25% of the present 50 normal cases. The *T* wave was inverted in *V*1, in the *rS*, *SR* and *Rs* group in 14 out of 19 cases (74%). The increased incidence of this finding in Class II cases of mitral stenosis cannot be regarded as significant except possibly where it occurs in association with an *Rs* complex, and where the *R/S* ratio is greater than unity. In the three of the 19 cases (16, 23 and 41) the *T* waves were inverted from *V*1 to *V*3. One of these cases was associated with an *rS* and the other two with either an *RS* or *Rs* complex in *V*1. However, these three records may have been influenced by the effects of digitalis therapy.

TABLE VIII.

*Mean Height R, S, R/S in V*5, *V*6.

Lead.	Group.				
	R, *S* or *R/S*. (Millimetres.)	*rS.*	*RS*, *Rs.*	"*RSR.*"	*R*, *qR.*
*V*5	*R*	11·7	9·1	13·2	11·9
	S	1·14	1·7	4·44	9·7
	R/S	10·3	5·35	2·97	1·22
*V*6	*R*	8·45	6·0	9·20	8·9
	S	0·64	0·6	2·49	6·1
	R/S	13·2	10·0	3·69	1·46

The "*RSR*" or incomplete right bundle branch block pattern seen frequently in Class III was associated with definite *T* wave inversion in 18 out of 22 cases (87%). Here the *T* waves were inverted more extensively; in some cases a shallow inversion was seen extending as far as *V*5.

*The QRS Patterns in Standard Limb Leads and V*1. Campbell (1952), in an editorial comment in a recent number of the *British Heart Journal*, remarked: "It has long been clear to me, and no doubt to many others, that extreme right axis deviation (large *S*1 and *R*3 with insignificant *R*1 and *S*3) is common in many forms of pulmonary stenosis and other congenital heart disease, much rarer in mitral stenosis (where a common finding is a small *R* wave in lead 1 and a larger *R* wave in leads

2 and 3) (the *rRR* type) and quite unusual in chronic pulmonary disease." The findings here would agree with this statement where an *rRR* combination has been found in 57% of the ventricular complexes of the standard leads. Campbell further points out that the *R*/*S* ratio in *V*1 increases from a normal value (0.5) in mitral stenosis mainly owing to a reduction in the size of *SV*1 and not to an increase in the size of *RV*1. This is contrasted with cases of congenital pulmonary stenosis, in which the *R*/*S* ratio increases as a combined effect of the increase in *RV*1 and a reduction in *SV*1. It is implied that this is unusual in mitral stenosis. The *R*, *qR* group (Class IV) in this series does not support this claim where *RV*1 has attained the height of 17 millimetres with an average of 8·7 millimetres for the group.

Correlation of Electrocardiographic and Physiological Findings

What conclusions can therefore be derived from the electrocardiogram concerning the degree of pulmonary hypertension and indirectly of right ventricular enlargement? Our findings have confirmed those of Johnson *et alii* (1950) that significant pulmonary hypertension can occur without the electrocardiographic pattern of right ventricular hypertrophy. This is demonstrated in six out of ten patients of Class II (Cases 2, 5, 8, 10, 12, 13), who had raised pulmonary artery pressures, but a normal electrocardiographic pattern with *rS* complexes and inversion of the *T* wave in *V*1.

TABLE IX.

Mean Values and Range of Mean Pulmonary Artery Pressure and Pulmonary Arteriolar Resistance in Relation to Electrocardiographic Evidence of Right Ventricular Hypertrophy.

Group.	*rS* (*V*1).	*RS*, *Rs* (*V*1).	"*RSR*" (*V*1).	*R*, *qR* (*V*1).
Mean P.A.P.[1] (millimetres of mercury)	27·6	43	41·6	61
Range P.A.P. (millimetres of mercury)	10·45	24–52	23–72	38–88
Mean P.A.R.[2] (dynes per sec. per cm.$^{-5}$) ..	230	425	580	970
Range P.A.R. (dynes per sec. per cm.$^{-5}$) ..	63–487	213–683	139–1494	567–1933

[1] Pulmonary artery pressure.

[2] Pulmonary arteriolar resistance.

Table IX shows the mean values and the range of the mean pulmonary artery pressure and pulmonary arteriolar resistance in patients of the various electrocardiographic groups. Progressive increase of both factors occurs from one group to the next; but the range of variation is great and any correlation between these two factors and electrocardiographic evidence of right ventricular hypertrophy is of little significance. As pulmonary artery pressure is the product of pulmonary flow and total pulmonary resistance, both dependent on variables such as mitral valve area, cardiac rhythm and the volume elasticity relationships of the pulmonary vascular bed, it is not surprising that so little correlation occurred.

An *RS* or *Rs* pattern in *V*1 associated with *T* wave inversion from *V*1 to *V*3 appears to be a reliable index of moderate pulmonary hypertension and presumably of right ventricular enlargement. An *R* or *qR* complex in *V*1 can be accepted without hesitation as indicating both advanced pulmonary hypertension and definite right ventricular hypertrophy.

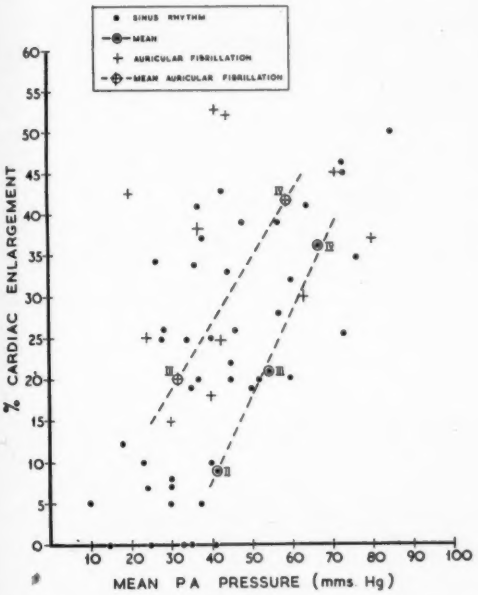
Incomplete right bundle branch block (an "*RSR*" complex in *V*1 of less than 0·12 second and intrinsicoid deflection greater than 0·03 second) was the predominant complex in Class III, in which mean pulmonary artery pressure and pulmonary arteriolar resistance were considerably raised. This electrocardiographic pattern therefore probably indicates both increased pressure and resistance in the pulmonary artery, and as cardiac enlargement was considerable in this class (*vide infra*) it may also be taken as evidence of right ventricular hypertrophy. Mounsey (1952), utilizing lead *V*3*R* in a series of cases of severe pulmonary emphysema, has presented evidence to suggest that the *RSR* pattern of incomplete right bundle branch block is a transitional stage between the normal *rS* and the *qR*, *R* pattern of advanced right ventricular hypertrophy.

We consider therefore that with increasing pulmonary hypertension the electrocardiogram does assume a more right-sided preponderance.

Radiological Findings

The effect of mitral stenosis on the X-ray configuration of the heart is well known (Steel, 1929; Parkinson, 1936; Master, 1942). With progressive mitral valve obstruction, the left auricle enlarges both posteriorly and to the right, until the normally clear retrocardiac space is partially or completely obliterated. In the postero-anterior view this chamber comes to form the upper portion of the right border of the cardiac silhouette, while the enlarged left auricular appendage may be visible below the main pulmonary artery prominence. The right ventricle in normal subjects is entirely anterior, extending to the diaphragm below and to the chest wall anteriorly. As this ventricle hyper-

trophies the heart is rotated in a clockwise direction around its long axis, the left ventricle being displaced posteriorly. The enlargement of the right ventricle is seen preferably as a change in contour of the left border of the heart shadow in the left oblique position. At the same time the pulmonary artery shadow becomes more prominent, owing partly to cardiac rotation and partly to increasing pressure with dilatation of the artery.



GRAPH II.

Comparison of percentage cardiac enlargement with mean pulmonary artery pressure in patients with and without auricular fibrillation. The mean values for each functional class are shown.

Cardiac Enlargement

The mean transverse diameter of the heart for Class II was 131 (118 to 147) millimetres, for Class III 147 (112 to 175) millimetres, and Class IV 156 (134 to 191) millimetres. The individual findings were compared with the normal values derived from the tables of Ungerleider and Clark (1939). If an increase of 20% in heart size is accepted as significant, then in two cases from Class II, in 19 from Class III and in 16 from Class IV the heart was enlarged. Cardiac enlargement is thus exceptional in Class II, frequent in Class III and almost invariable in Class IV. This is also reflected in the mean values of the cardio-thoracic ratio for each class, which were 0·49 (0·43 to 0·54), 0·58 (0·47 to 0·61) and 0·60 (0·50 to 0·71) respectively. There was a practically linear relationship between the cardio-thoracic ratio and the percentage enlargement.

The cardiac enlargement has been compared with the pulmonary artery pressure in Graph II. An approximately linear relationship is shown. This graph illustrates two interesting features. First, significant pulmonary hypertension (up to 40 millimetres of mercury) can be present without measurable cardiac enlargement. Second, patients in Class III with auricular fibrillation tended to have lower pulmonary artery pressures than patients with comparable heart size with sinus rhythm. In Class IV, patients with auricular fibrillation had slightly larger hearts than those with sinus rhythm, but pulmonary artery pressures were only slightly lower (Table X and Graph II).

TABLE X.

Comparison of Transverse Cardiac Diameter, Mean Pulmonary Artery Pressure and Pulmonary Arteriolar Resistance in Patients With and Without Auricular Fibrillation. (Mean Values)

Observation.	Class III.		Class IV.	
	Auricular Fibrillation.	Sinus Rhythm.	Auricular Fibrillation.	Sinus Rhythm.
Transverse diameter (millimetres) ..	153	147	166	156
Cardio-thoracic ratio ..	0·54	0·54	0·64	0·60
Mean P.A.P.[1] (millimetres of mercury)	32	57	59	68
P.A.R.[2] (dynes per sec. per cm.$^{-5}$)	366	400	1112	1029

[1] Pulmonary artery pressure.
[2] Pulmonary arteriolar resistance.

Right Ventricle

It was difficult to detect minor degrees of right ventricular enlargement even in the left oblique view. The right auricle frequently contributes to the upper portion of the anterior cardiac border in this view, while the lower border may be obscured by the breast shadow. Greater right ventricular enlargement can be seen as an increase in convexity of this portion of the cardiac silhouette. It is our impression that in pure mitral stenosis the right ventricle often contributes markedly to the backward displacement of the left ventricular border across the spinal column shadow.

Left Auricle

The size of the left auricle was recorded by a system of notation (1+, 2+, 3+). The sign "1+" denoted slight enlargement where the barium was deflected backwards in a short abrupt arc and the degree of displacement was not great. Further enlargement of the

left auricle usually caused a more diffuse backward bowing of the barium, although this was not invariable. A left auricle which was easily visible on either side of the cardiac contour and associated with cardiac enlargement was designated " 3+ " (Figure IV).

Pulmonary Artery and Lung Fields

A similar system of notation was adopted for the size of the pulmonary artery (Healey *et alii*, 1949—Figure V). The term " pulmonary artery convexity " refers to the localized prominence seen below the aortic knob on the

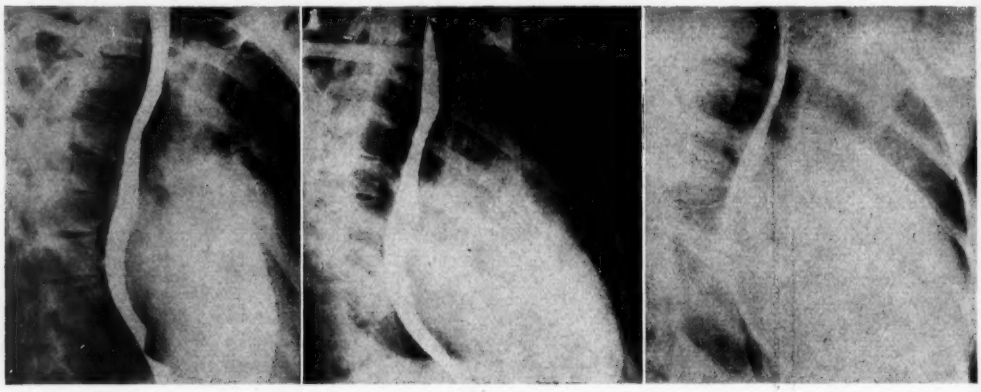


FIGURE IV.
Left auricular size (1+ to 3+).

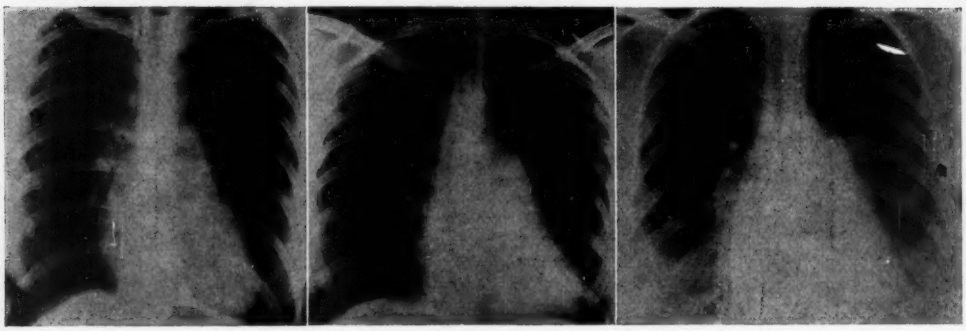


FIGURE V.
Pulmonary artery size (1+ to 3+).

In none of the present cases was the left auricle more than moderately enlarged. This was due mainly to the fact that the cases in this series were selected for mitral valvotomy, for until recently pronounced left auricular enlargement has been considered a contra-indication to this procedure. In most cases in Class II " 1+ " enlargement was present, but " 2+ " to " 3+ " enlargement occurred equally among Class III and Class IV patients. Auricular fibrillation was usually associated with a larger left auricle.

left cardiac border; this is composed of the main pulmonary artery and the proximal portion of the left pulmonary artery (Robb and Steinberg, 1939).

Wood (1952) reemphasized the importance of increasing prominence of the pulmonary artery convexity as pulmonary hypertension progresses. This has been our experience; in no case in Class II has more than grade I enlargement been present, and the most prominent pulmonary artery convexity has been seen in Class IV patients with a mean pulmonary

artery pressure greater than 50 millimetres of mercury. Of equal importance as a sign of pulmonary hypertension is an increase in translucency of the outer lung fields. The ramifications of the pulmonary arteries can be followed only with difficulty beyond the inner half of the lung fields. Beyond this, translucency increases and the lung fields take on an oligæmic appearance. Only in extreme cases of pulmonary hypertension in our series was this feature present.

Pulmonary venous congestion is seen radiologically as a fine granular density extending in a flare fashion from the hila of the lungs. It is said to be evidence of high left auricular and pulmonary venous pressure. No example was seen in Class II and only a few cases occurred in the other classes. As acute pulmonary venous congestion proceeding to acute pulmonary œdema can occur at almost any time in the life history of mitral stenosis, one would not expect this radiological sign to be restricted to any one functional category.

Hæmosiderosis was seen in only one case in this series (Case 40).

SUMMARY AND CONCLUSIONS

Electrocardiographic and X-ray data of 57 patients with mitral stenosis who have all been submitted to cardiac catheterization are presented.

In these patients pulmonary hypertension is always present for some time before it can be detected by either electrocardiographic or X-ray changes, and the initial signs of right ventricular hypertrophy rarely occur until the mean pulmonary artery pressure rises above 40 millimetres of mercury. At this stage the mitral valve area is usually about 1·0 to 1·5 square centimetres. As the valve area decreases, cardiac enlargement and pulmonary hypertension develop side by side and their effects are reflected in progressive changes in the electrocardiogram and X-ray configuration of the heart.

Patients in functional Class II show little if any cardiac enlargement, and the electrocardiographic changes are usually limited to the *P* waves, which are broad, bifid and sometimes flattened. As the disease becomes more severe, the *P* waves become broader and higher and tented in contour, and these changes are seen more frequently in leads 2, 3 and *aVF*. In advanced cases, the *P* wave usually exceeds 0·12 second in duration and 2·5 millimetres in height—indications of considerable right auricular hypertrophy.

Right ventricular hypertrophy as determined electrocardiographically is unusual in Class II. The R/S ratio in $V1$ is below unity and auricular fibrillation is not encountered. The earliest signs of right ventricular enlargement are an increase in the R/S ratio in $V1$ (usually caused by a progressive diminution in the depth of the *S* wave) and an incomplete right bundle branch block pattern in $V1$ (RSR). The most severe grades of pulmonary hypertension are usually associated with a qR or R complex in lead $V1$, the tracing in a small number of cases resembling that seen in congenital heart disease with right ventricular preponderance.

Class II patients rarely show any increase in heart size, and the largest hearts are seen in Class IV. Certain evidence has been presented that disproportionate cardiac enlargement occurs in those cases in which auricular fibrillation is present, suggesting that this is a deleterious and inefficient form of cardiac function. Concurrently with the increase in the transverse diameter of the heart, the pulmonary artery convexity increases in size, and in Class IV patients becomes a prominent landmark on the left cardiac border. This sign is regarded as important evidence of advanced pulmonary hypertension. With prolonged pulmonary hypertension, the peripheral portions of the lung fields become more translucent.

Fluoroscopy has been of limited value. Although gross mitral insufficiency can be easily detected, minor grades have been most difficult to assess. Our ability to determine the size of individual chambers of the heart has been limited, although some general assessment of left auricular size has been gained, after repeated fluoroscopic screening, by comparison with evidence obtained during operation.

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CEREBRAL ANGIOMATOUS MALFORMATIONS[1]

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THIS discussion concerns the congenital anomaly known as angioma, angiomatous malformation or arterio-venous aneurysm—a variety of the hamartoma of Albrecht (1904). The anomalous arrangement of cerebral blood vessels is a malformation and not a new formation; it is a *Missbildung* or *Fehlbildung*, not a *Neubildung*. It is distinct from capillary telangiectasis, cavernous angioma, the Sturge-Weber syndrome and capillary hæmangioblastoma (a true neoplasm), the pathological features of which are said to be well established (Northfield and Russell, 1951). In the case of capillary telangiectasis and cavernous hæmangioma, however, this is by no means certain (Wyburn-Mason, 1943; Hayward and Reid, 1949).

Although, as reference to Liddell and Scott's (1909) lexicon shows, the Greek word ἁμαρτία and its verb give a nice notion of a freakish and errant nature, the term hamartoma has not found favour with clinicians. Dandy (1928*a*), who was one of the first clearly to perceive the nature of the lesion, called it an arterio-venous aneurysm, and he has been followed by Olivecrona and others; but it must be understood that a direct communication between artery and vein is not meant, for except in the cavernous sinus region, where trauma is the usual cause, this is almost unknown in the cranial cavity. One of Dandy's cases, in which arterio-venous linkage by means of an anomalous branch of the middle cerebral artery was the only apparent lesion, is possibly the only verified example of such a communication. As he points out, the cavernous sinus arrangement is not duplicated elsewhere in the body, let alone within the cranium.

Cushing and Bailey (1928) distinguished between *angioma venosum* and *angioma arteriale*. To them, however, *angioma arteriale* was synonymous with the arterio-venous anomaly, and they admit the term's inadequacy. No convincing example of a pure arterial lesion has in fact been described. There is evidence of the existence of a pure venous angioma (Cushing and Bailey, 1928; Dandy, 1928*b*; Worster-Drought, 1951). An apparently unique angiogram of a vascular malformation, in which only venous channels could be seen, was obtained by Curtis (1949). He refers to the possibility of one previous demonstration of such a condition by Green and Arana. A pure venous lesion, however, is exceedingly rare, and in several possible cases Cushing and Bailey found it "impossible to be sure of their precise nature". There is little doubt that lesions thought in the past to be composed of veins alone were arterio-venous ones. Olivecrona and Riives (1948), who met with none, point out that the difference is physiological and depends on the extent of the arterial supply. If this is sufficient to give the blood in the malformation an arterial colouring, it should be classed as an arterio-venous aneurysm; the differentiation can be made only *in vivo*. The writings of Cushing and Bailey and of Dandy show that they held much the same opinion. Those who, at operation, have seen a typical lesion must agree with the former authors that "it is improbable that the post-mortem appearances can give more than a faint idea of what the actively pulsating snarl of vessels may be like during life". Others have stated that they were unable to make a histological distinction between arteries and veins; and embryological studies, helpful in the understanding of intracranial aneurysms, have not been fruitful (Sugar, 1951). Adjectives such as racemose, serpentine and cirsoid, being merely descriptive of shape and form, have strictly limited pathological and clinical value.

It remained for cerebral angiography further to demonstrate the dynamic pathology of these lesions. Bull (1949) has reviewed this development, stressed the advantage of the percutaneous method of puncture of the carotid artery, and paid tribute to the pioneers. So it is that our more exact knowledge of these lesions is due to contrast radiography and to neurosurgeons such as Olivecrona and Norlén, who have made full use of it.

Among 1522 cerebral tumours in the material of Cushing and Bailey (1928), only nine were

[1] Received for publication on January 14, 1953. The substance of this paper was read at a meeting of the Royal Australasian College of Physicians, Perth, October, 1951.

diagnosed. With the increasing use of the percutaneous method many more cases have been discovered. In their classical contribution Olivecrona and Riives (1948) reported 60 among 3206 verified cerebral tumours. They quote earlier continental literature which is not readily available. They refer, when necessary, to cases described in a monograph of which Olivecrona was part author, and which has long been out of print (Bergstrand, Olivecrona and Tönnis, 1936). In 1949 Olivecrona was able to report 83 cases among 3500 cerebral tumours (*The Lancet*, 1949). Of these, 49 patients had been subjected to operation. Norlén (1949) has published the results of operation upon ten patients. Wylie McKissock (1950) has given his experience based upon 39 cases, more than half of which were diagnosed in the previous three years. In this series 13 patients were submitted to operation. Twelve survived, and post-operative angiograms showed two with incomplete excision, while in ten no trace of the angioma remained. Bassett (1951) has described 18 cases.

An article by Trupp and Sachs (1948) illustrates how confusing the clinical picture can be without the aid of angiography.

There has been considerable uncertainty about treatment. The earlier operators considered the mass irremovable. Cobb Pilcher (1946) was one of the first to attempt radical removal of an angioma. Few now believe that the method of electrocoagulation advised by Trupp and Sachs could be effective. Olivecrona is convinced that decompression, X-ray therapy and carotid artery ligation are likewise ineffective. He and Riives record how they gradually came to the conclusion that the choice lay between removing the angioma and leaving it alone. In his hands the results of carotid artery ligation were bad, and he considers that it is dangerous. Wechsler, Gross and Cohen (1951) seem to have been fortunate with this procedure.

This paper is based on a study of eight patients. The first five were discussed by Mr. J. P. Ainslie at a meeting of the Neurosurgical Association of Australia in June, 1951.

The Lesion

As suggested, the cerebral anomaly is an arterio-venous one. Between the arterial and venous components lies a tangled mass of abnormal blood vessels, and this tangle is the angioma proper. It has feeding arteries and emptying veins. Because the blood is quickly shunted into the emptying veins, these may pulsate and contain arterial blood. It has often been shown at operation that compression of a draining vein makes the angioma swell. This is a warning to the surgeon not to tie or damage such a vein until all entering arteries have been secured. The mass and its emptying veins then collapse, and the blood in the veins becomes dark. The lesions occur mainly in the field of the anterior or middle cerebral arteries. The posterior cerebral artery or an external carotid branch may contribute. The arteries commonly enter at the apex of a pyramid or cone, going down to the ventricular wall. The larger base usually, but not always, lies over the cortex. So great is the diversion of blood to the angioma that unaffected areas of the brain are starved of their supply. Vessels, thin or invisible in the preoperative angiogram, may be seen to stand out in one taken after excision of the mass. On the other hand, abnormally dilated vessels assume a more normal calibre. Compared with these facts, the importance of the histology of the lesions is slight. Little can be added to the statement of Olivecrona and Riives that " the tangle of blood vessels interposed between arteries and veins may have the character of arteries or veins; most of the vessels, however, are undifferentiated and of a pathologic structure ".

The Clinical Picture

Symptoms of an angioma are usually delayed until the second or third decade of life or later. The most common are epilepsy, frequently focal but often general, and subarachnoid hæmorrhage. Their combination in one patient is almost conclusive. Intracerebral hæmorrhage with hemiplegia may occur. Sensory defects and hemianopia may be found. A bruit may be pathognomonic. It was heard in two of our cases, but in only about 15% of Olivecrona's large series. Headache is common; rarely characteristic, it is often slight or absent. Migrainous episodes with or preceding focal seizures are to be suspected. The first patient in the present paper illustrates this. Sometimes the course imitates that of a slowly-growing tumour, but persistently raised intracranial pressure is rare. In those cases in which epilepsy is a feature, if air encephalography without angiography is undertaken, a diagnosis of cerebral atrophy is apt to be made, for there may be some ventricular dilatation on one or both sides. Progressive mental deterioration has often been noted. This may be due to the repeated cerebral hæmorrhage observed in some cases, but may occur in the absence of vascular accidents. In the latter cases exhaustion of normal blood channels, mentioned earlier, is a possible cause.

RESULTS OF TREATMENT

A study of the literature and of my own cases confirms the conclusions reached by Olivecrona, who has had the largest experience of this lesion. Admittedly the present series is by contrast very small, but consideration of the angiograms of these eight cases, and of the malformations themselves at operation, supports the main conclusion—namely, that anything less than removal is likely to be ineffective. The operation is a formidable one, and it should not be urged in the case of every patient who has had only one or two fits. Careful planning by carotid angiography, if necessary bilateral, is essential. Much depends on the situation and accessibility of the lesion. Post-operative hemiplegia and, in lesions in the dominant hemisphere, aphasia, are great risks. Yet so serious is the plight of many patients that operation on a large lesion in the dominant hemisphere may be justified. The outcome is always unpredictable, and this justifies at least consideration of operation in every case. As with the successful removal of cerebral tumours, epilepsy may continue to occur. In our own series, if the fatality is left out of account, no patient has been the worse for operation. It is submitted that, with the probable exception of the patient in whom removal was incomplete, the occurrence of the worst symptom, hæmorrhage, has been certainly prevented. In one patient a maniacal and dangerous state following epileptic attacks seems to have been abolished, at the cost of mild aphasia.

REPORTS OF CASES

CASE I.—E.R.N., a male patient, aged forty years, a contractor, was examined on October 31, 1949. Twenty-two years before he had suffered a head injury, but was soon back at work without seeking medical advice. One year later he had a major epileptic fit, and he had several more in the next two years. Medical treatment seemed to relieve these because, except for one which occurred six years before he came for examination, he had no more. For seventeen years he suffered attacks of numbness in the right hand and a "muddled brain". During these attacks he seemed not to hear what was said to him. Headache, always in the left temporal region, often accompanied these attacks. Five months before examination he suffered an attack of very severe headache together with numbness in the right hand and the lower part of the forearm lasting for forty-four hours. This was followed by a throbbing noise in his head, which had recurred intermittently ever since. Several further less severe attacks occurred, and the patient had great difficulty in concentrating and carrying out his work.

No abnormality was found in the skin, heart, lungs or abdomen. The systolic blood pressure was 135 millimetres of mercury and the diastolic blood pressure 80 millimetres. The urine was normal. In the skull a bruit was heard over the left upper carotid region and in the temple. It could also be heard, to a lesser degree, over the same area on the right side. Left, but not right, carotid pressure caused it to disappear. The ocular fundi, pupils and cranial nerves were normal. The visual fields were full. No abnormal motor or sensory signs could be demonstrated. The tendon and superficial abdominal reflexes were active and equal. The plantar reflexes were of flexor type. A plain X-ray film of the skull revealed some erosion of the inner table, with flecks of calcium extending inwards, in the left temporo-parietal region.

On November 15, 1949, a left carotid angiogram showed a large angioma in this region. The anterior cerebral artery was not filled. An antero-posterior projection was not made. He accepted the risk of operation, saying that he could no longer endure the crippling headaches. Unfortunately he died from uncontrollable hæmorrhage at operation the next day.

It was later realized that further information might have been obtained from a right angiogram, and that filling of the left anterior cerebral artery might have resulted from this. In all subsequent cases an antero-posterior exposure was made. Olivecrona describes how, through neglect of this procedure in one of his earlier cases, he actually operated at first upon the wrong side.

CASE II.—W.G.T., a male subject, aged nineteen years, a shop assistant, was admitted to hospital on August 21, 1950. The past and family history contained nothing of note. He had never suffered from headaches. On August 5, 1950, sixteen days before his admission to hospital, he had mild frontal headache which almost disappeared in two hours. Later that evening it recurred and became increasingly severe, although he had rested during the day. Within half an hour he was heard to give a cry and was seen to collapse in his chair. He remembers no more until three days later, when he awoke to find himself in hospital in the country town in which he lived. His relatives stated that he was drowsy, non-cooperative and incoherent during the three days. A medical man was not called for two days. His doctor then examined him and reported that he was stuporose, responding only to shouts. The temperature was 37·2° C., the pulse rate was 80 per minute, and the respiratory rate 20 per minute. The urine contained no albumin or sugar. The systolic blood pressure was 140 millimetres of mercury and the diastolic blood pressure was 90 millimetres. Neck stiffness was present. The reflexes were equal and active and there appeared to be no loss of power or sensation. On August 7, lumbar puncture produced grossly blood-stained fluid under increased pressure. On August 8 his mental acuity and alertness returned. He still complained of headache, chiefly frontal. On August 17, as the headache persisted, a second lumbar puncture was performed. Xanthochromic fluid under normal pressure was obtained. He was sent to Perth.

On admission to hospital he seemed well, complaining only of mild frontal headache, more severe on the right side. He was a well-built, cooperative lad. No neck stiffness was present. The skull was normal to percussion and there was no bruit. The ocular fundi were within physiological limits. The visual fields, pupils and cranial nerves were normal. No abnormality was found in the motor or sensory systems,

The tendon and superficial abdominal reflexes were equal and active, and the plantar reflexes were flexor in type. Examination of the heart and other organs revealed no abnormality. The hæmoglobin value was 13 grammes *per centum*. The blood failed to react to the Wassermann and Kahn tests. A plain X-ray film of the skull revealed no abnormality.

A right carotid angiogram on August 24 gave the following information: The early antero-posterior view showed (*a*) slight displacement across the mid-line of the anterior cerebral artery, (*b*) an extremely low take-off of the fronto-polar artery, (*c*) a vessel nest at the termination of the fronto-polar artery. In the late antero-posterior view a nest of vessels with enlarged venous channels was seen. The early lateral view showed (*a*) an incomplete shadow of the fronto-polar artery, and (*b*) the same vessel nest. The late lateral view showed dilated venous channels in the region of the angioma.

On September 8 the angioma was removed at operation. Convalescence was uneventful apart from slight hæmatoma formation under the skin flap. On September 26 a post-operative angiogram showed that the mass had been completely removed. The pathologist's report upon the specimen was as follows:

> A congenital angioma or arterio-venous shunt, with large vessels, which are now slit-like, due to the compression of the hæmorrhage around them. The walls of the vessels are thicker than normal and show intima and thick muscularis. Dilated vessels can also be seen in the neighbouring brain tissue. There is one thick walled vessel which I would regard as an artery. It has cushion-like proliferation of its intima, conspicuous internal elastic lamina and thick muscularis. I would consider the majority of the vessels in this section, however, to be veins.

The patient remained well for the next twenty months, gaining 2·5 centimetres in height and six kilograms in weight. On April 24, 1952, he again presented himself at the clinic, having suffered from two epileptic fits the week before. He seemed well and his activities were unrestricted. Anticonvulsant medication had been commenced. His doctor reported on August 6 that he had had no more fits.

Case III.—J.W., a male patient, aged forty-eight years, a watch-repairer, was admitted to hospital on March 12, 1951. The family history was not relevant. Seven years earlier he had suffered a severe pain arising suddenly in the back of his head and in his neck. He was in a Royal Australian Air Force hospital for two weeks and then returned to duty. Lumbar puncture was not performed. He had also had mild generalized headache for years. This had never prevented him from working, and had always been relieved by aspirin, phenacetin and caffeine.

Two weeks before his admission to hospital he had a sudden pain in the back of the head and neck similar to that of seven years before. With difficulty he continued to work while taking an analgesic drug. Frequent doses were necessary. On the day of his admission to hospital he was driving himself to work when the headache became unbearable. He reached a doctor's surgery, where he vomited and was said to be disorientated. Admission to a country hospital followed. Blood-stained cerebro-spinal fluid was obtained at lumbar puncture and he was flown to Perth the same day.

The patient was conscious and rational, but he obviously had severe headache. The systolic and diastolic blood pressures were 130 and 80 millimetres of mercury respectively. The urine was normal. The temperature was 36·5° C., the pulse rate 84 per minute. The heart, lungs and abdomen seemed normal. The ocular fundi and visual fields were normal. Very slight diminution of all forms of sensation was present on the right side of the face. The cranial nerves were otherwise normal. Slight patchy diminution of light touch, heat and cold and pin-prick sensation was noted over the whole of the right side. Postural and vibration senses were normal. Tone, power and coordination were normal in all limbs. The tendon and superficial abdominal reflexes were equal and active. The plantar reflexes were flexor in type. The hæmoglobin value was 12·8 grammes *per centum*. No abnormality was seen in a plain X-ray film of the skull.

On March 15, a left carotid angiogram was unsuccessful; a right carotid angiogram was normal. After this, headache again became severe and lumbar puncture produced yellow fluid at a pressure of 250 millimetres of water. On March 22 he was well and a left carotid angiogram was taken, the radiologist's report being as follows:

> Antero-posterior projection: the arterial phase shows—
>
> 1. A nest of vessels between the normal distribution of the anterior and middle cerebral arteries.
> 2. A large vessel apparently arising from the internal carotid just before its bifurcation and apparently entering the vessel nest. It is in the position of the anterior choroidal artery. The later phase shows dilated venous channels running from the vessel nest across the mid-line. The lateral projection shows, in the arterial and late arterial phase, the vessel nest to be in the posterior parietal region in the neighbourhood of the lateral ventricle; and the capillary phase shows a blush which has a shape not unlike the posterior part of the lateral ventricle. The oblique projection shows the mass to be larger than suspected in the other views.
>
> *Finding.*: Large arterio-venous aneurysm probably arising from the anterior choroidal artery. Intra-ventricular rupture may have occurred in this case.

The lesion was considered to be inaccessible to surgery. On his discharge from hospital on April 6, the patient was ambulant and symptomless. On August 16, 1952, he stated by letter that he still suffered fairly frequent headaches, but that these had not been severe enough to prevent him from working.

Case IV.—M.K-W., a female patient, aged thirty-nine years, a housewife, also from the country, was admitted to hospital on April 2, 1951. The family and past history was not relevant. She had no symptoms until an attack of epilepsy seventeen months previously.

In November, 1949, she suffered a generalized epileptic fit, occurring in her sleep. Her husband found her with her eyes glazed, foaming at the mouth and making jerking movements of all her limbs. She stopped this a few moments later and then appeared to be normal. She herself is unconscious of that episode. Six weeks before her admission to hospital, while sitting at the breakfast table, she suddenly had a severe sharp generalized headache. She managed to drag herself to her bed, where she lay down. She remembered her young son asking if he should send for the doctor and herself agreeing that he should.

She then remembered nothing more except odd snatches of conversation for five days. She was told later that she had been taken to hospital and was never at any time unconscious. She was noisy but reasonably rational, and was never incontinent of urine or fæces. Suddenly, five days later, she became aware of her surroundings and noticed that her left upper and lower limbs were very weak. She had to lift her left leg before she could get out of bed and had to be helped before she could take any steps. The left side of her visual field was all "blacked out" and she found herself bumping things accidentally.

Gradually the power in the left upper and lower limbs returned, and she considered that she had fully recovered when she was admitted to hospital. At first she said that her field of vision was again normal, but later she said that she was conscious of the defect found. She had no headache.

The patient was a thin, middle-aged woman, mentally alert and giving a clear history. The systolic and diastolic blood pressures were 140 and 90 millimetres of mercury respectively. The pulse rate was 76 per minute. No albumin or sugar was found in the urine. No abnormality was found in heart, lungs or abdomen. The hæmoglobin value was 12·1 grammes *per centum*. Ocular examination, three days before her admission to hospital, revealed an apparently complete left homonymous hemianopia. One day after her admission visual acuity was 6/5 in both eyes. The pupils were equal and active, and the fundi were normal. The homonymous hemianopia was now a left upper quadrantic one, and she herself considered that the field had improved. The cranial nerves were otherwise normal. Full power and coordination were present in all limbs, and the tone was normal. No impairment of any form of sensation was present. The tendon reflexes were all over-active but equal. No superficial abdominal reflexes could be elicited. The plantar reflexes were both flexor in type. X-ray pictures of the skull and chest were normal.

A right carotid angiogram on April 5, 1951, gave the following information:

> The right anterior cerebral artery was unfilled. A large tortuous overfilled middle cerebral artery led to an extensive angiomatous mass which penetrated deeply into the brain. Large exit veins opened into the superior sagittal sinus.

Increased knowledge and experience since the first case suggested that left carotid angiography should be carried out. This was accordingly done on April 12, with the revelation that the right anterior cerebral artery had been filled from the left side, and that it supplied a feeding vessel to the mass. This information was important. The lateral view showed a normal left cerebral vascular supply, superimposed on which was the shadow of the grossly dilated right anterior cerebral artery. Operation was performed on this day. As the findings illustrate the importance of a complete angiogram, details of the operation are worth giving.

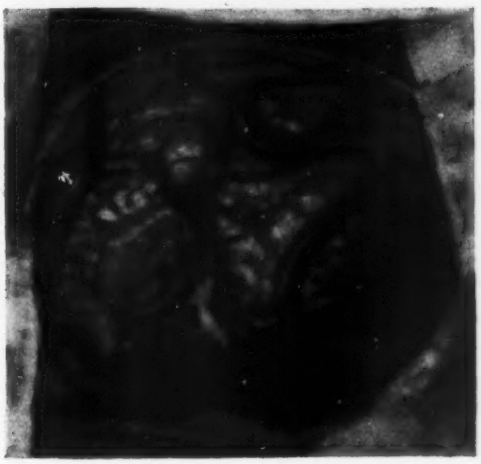

FIGURE I
Case IV: angioma as seen at operation

A skin flap was turned back, the right parieto-occipital area being exposed widely, and a large bone flap was turned down, based on the posterior part of the temporal muscle. The dura was then reflected and numerous fine adhesions were encountered between the large vessels supplying the angioma and the dura. These were carefully divided by sharp dissection. The angioma was then exposed in the posterior part of the exposed brain (Figure I). It measured about 3·5 centimetres in diameter and was roughly circular. The main blood supply came from the grossly distended middle cerebral artery, which was about four millimetres in diameter. This main vessel coursed across the anterior part of the mass, and there appeared to be a direct communication between it and a greatly dilated vein. Close to this area was a large amount of greenish blood-staining, due to the recent hæmorrhage. Several other large vessels were seen disappearing into the angioma. All these vessels were tied and divided

between ligatures, but the blood supply to the angioma did not appear to be greatly diminished until the branch from the anterior cerebral artery, which entered the postero-medial part of it, was ligated. After this, the blood of the numerous vessels comprising the angioma became much darker. It was then carefully removed, all vessels being secured by under-running with silk sutures as they appeared. There was no undue blood loss during this procedure, and at the end of this stage the bed of the mass was quite dry. The walls of the resulting cavity were then overlaid with "Oxycel" gauze, and before closure of the dura, hæmostasis appeared complete and the veins leading from the cavity were now in a collapsed state. The dura was then closed completely and the edges were sutured to the overlying pericranium. The bone flap was replaced and sutured in position, and the wound closed in the usual manner.

The pathologist's report upon the malformation removed at operation was as follows:

> Arteriovenous aneurysm or angioma. The section shows portion of the brain with transverse sections of numerous thick-walled vessels. In spite of their thickness these vessels do not show an internal elastic lamina or a muscularis. I would call them veins. They are composed of a thin endothelial layer followed by acellular collagen fibres which contain only a few widely separated smooth muscle fibres. The increase in thickness is due to proliferation of the connective tissue. The surrounding brain tissue shows recent hæmorrhage and gliosis, some proliferation of capillaries in a circumscribed area, and probably also evidence of malformation.

The operative and post-operative courses were favourable. A post-operative right carotid angiogram on May 8, 1951, showed that the right anterior cerebral artery was now fairly well filled and not so dilated as before operation. It was seen that the whole mass had not been removed. However, the calibre of the middle cerebral artery was less, and there was no sign of the left efferent veins. She had been discharged from hospital, well, on April 31, and had been re-admitted for this angiogram. At a review of the ocular condition some days before her discharge, the left homonymous hemianopia was once more complete, but had partially cleared in the lower quadrants just before she left.

On October 11, 1951, she felt quite well except for a small discharging area at the summit of her scar. Later osseous infection at the site of the wound required further surgical intervention, but she was discharged from hospital, well, on February 8, 1952, and wrote on March 21 that she remained well and was able to do all her housework.

Case V.—D.C., a male patient, aged thirty years, a labourer, was admitted to hospital on May 7, 1951. The family history was unimportant and the past history was merely one of frequent epilepsy. He said that sixteen years earlier, when he was fourteen years old, he had fallen from his bicycle. He remembered the fall, but nothing more until he awoke in hospital at a farm school. He had generalized headache but no outward sign of injury. Two months later he had a fit which was witnessed. It began with a sensation that a draught was passing through his head, and he felt compelled to sit down. For a quarter of an hour, according to witnesses, he seemed aware of his surroundings but was unable to answer questions. He then lost consciousness, falling to the ground in generalized convulsions. This fit lasted a few minutes. Thereafter he had similar fits about once a month. His tongue was often bitten. A severe headache for some hours usually followed but after a sleep he felt well. Eighteen months before his admission to hospital he began to have, as well as the fits described, abortive fits which stopped short of convulsions. The same sensation as before was experienced. For two months the fits occurred twice a week. His wife confirmed this history, and added that, after a fit two weeks before he had become maniacal and she feared he would injure her. He had been taking a sodium phenytoin capsule of 0·1 gramme in the form of "Dilantin" four times daily for three years. Before that he had taken 65 milligrammes of phenobarbital three times daily.

On examination of the patient, he appeared physically fit and reasonably alert. He was rather slow of speech. His systolic blood pressure was 130 millimetres of mercury and his diastolic blood pressure 80 millimetres. The urine was normal. The temperature, heart, lungs and abdomen were normal. The skull was normal to percussion. On auscultation, however, a bruit was heard over the left anterior temporal region. No papillœdema or visual field defect was found. The cranial nerves were intact. Muscle tone, power and coordination were normal. No sensory defect was present. The tendon and superficial abdominal reflexes were active and equal. The plantar reflexes were flexor in type.

Two days after this examination he had a fit from which he quickly recovered. Three hours later another followed. He then became uncontrollable, shouting, hurling abuse and fighting anyone who tried to restrain him. Paraldehyde to a total of 28 millilitres, with 0·4 gramme of sodium phenobarbital, had to be given intramuscularly in one and a half hours in an attempt to quieten him. About five hours later he suddenly became normal and rational with complete amnesia since recovery from the first fit, which he remembered. The next day a left carotid angiogram demonstrated a very large angiomatous malformation on the left side. The anterior cerebral artery could just be seen. A huge, dilated middle cerebral artery led into the mass, and large efferent veins, appearing very early in the series, were seen (Figure II).

Although the lesion was in the dominant hemisphere, his plight was such that operation was considered to be justified. After intraarterial blood transfusion operation was carried out on May 17 and proved very difficult. Except for three large dilated veins, the lesion was mainly subcortical. In the ligating of a deep artery, the lateral ventricle was opened and the choroid plexus seen. No feeding vessel came from this. Convalescence was stormy. He had numerous fits, aphasia and right hemiplegia. Some fits were right-sided, some generalized. They ceased on May 28 when he was able to say "yes" and "no", to recognize people and to obey simple instructions. Spastic hemiparesis was still very evident.

On June 15 he was well enough to get up. He walked with an obvious dragging of the right lower limb. An angiogram on July 5 showed no sign of the angioma. The anterior cerebral artery was now well filled. The mass had been extirpated and the middle cerebral vessels, up to the point of ligature, were now of normal size. The anterior cerebral artery had taken over the supply of a large part of the parietal region (Figure III).

FIGURE II
Case V: left carotid angiogram before operation

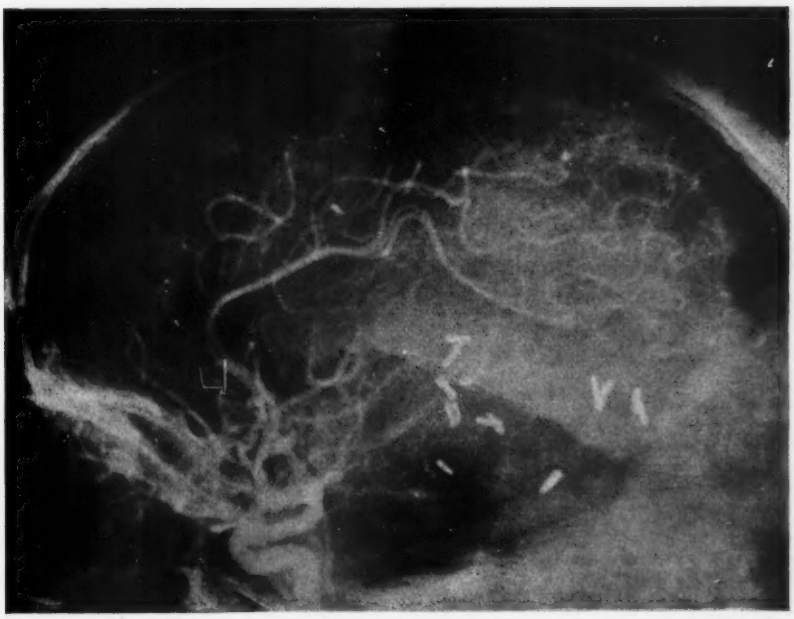

FIGURE III
Case V post-operative angiogram

The pathologist's report upon the section was as follows :

> This section through portion of the brain and meninges shows meningeal and cerebral hæmorrhages with numerous dilated vessels in the brain substance. Many are thick-walled and some sort of a media is recognizable in these. They are probably veins, however, since they show no internal elastic lamina. I find, in the literature, that such vessels have usually been regarded as veins, even when they are thick-walled. In that case they are supposed to become arterialized from the increased pressure exerted on them by the direct communication with an artery. Comparing the three sections I would say that only in Case 2 was I able to identify an artery definitely. One should also remind oneself of the special type of artery found in brain tissue ; it is certainly much more thin-walled than an artery of corresponding calibre in the trunk. The thinness is due to lack of media.

He was discharged to a rehabilitation centre on July 11. He was able to say only short sentences with some hesitation ; he read aloud with great difficulty and could write only the simplest sentences. The hemiparesis was much relieved, and he had only a slight limp. He was again in hospital between August 8 and 20 for treatment of a small stitch abscess. This soon cleared up. The aphasia had decreased, but was still obvious. On November 1 he attended hospital with his wife, who was well satisfied with his condition. He had performed light casual work. There had been no more fits. Continuous anti-epileptic treatment had, of course, been ordered. On December 26, however, his wife telephoned to say that he had had two epileptiform convulsions that morning. He did not visit the clinic until January 31, 1952. His wife, who was with him, said that he may have had one more fit, but she was not sure. On only one occasion had he become threatening, after taking alcohol at a party. The only other occasion on which his behaviour had been abnormal was when he flew into a rage because she had rebuked their daughter. He had been performing light work at a milk factory and had been absent from it only during the period when he had the fits. Conversation was almost normal for a few sentences, but he quickly tired and broke down. His wife said that he could do better in the quietness of their own home. Power in the right upper and lower limbs was good, being little below normal. On July 3, 1952, he was again examined. The position was much the same. He was engaged in casual farm work and was awaiting reemployment at the milk factory for the busy season. He had had no more fits.

Case VI.—R.C., a schoolboy, aged fifteen years, was examined on September 24, 1951. His father said that the boy had been well until after breakfast on that day, when he complained of occipital headache and vomited. He seemed slightly confused. The headache persisted. He had had infrequent slight headache for some years, but it had never prevented normal activity. His past history otherwise was unimportant, and his family history was irrelevant.

On examination, the patient was conscious and alert. He complained of moderate occipital and frontal headache. The temperature was 36·6° C. and the pulse rate 84 per minute. The systolic and diastolic blood pressures were 130 and 80 millimetres of mercury respectively. No abnormality was found in the skin, heart, lungs or abdomen. There were no enlarged glands. Neck stiffness was present. The ocular fundi, pupils and cranial nerves were normal. There was no motor weakness or dystonia. The reflexes were all normal. He was admitted to a private hospital. At lumbar puncture, the cerebro-spinal fluid was under a pressure of 220 millimetres of water and uniformly pink-coloured. After this he said that his headache was completely relieved. On September 27 he was transferred to the Royal Perth Hospital and a left carotid angiogram was taken. This disclosed a cluster of abnormal blood vessels at the inferior surface of the left frontal lobe. For obvious reasons a vascular meningioma was very unlikely, but an exploratory operation was considered to be justified. This was carried out on October 4, and no tumour was seen. It was deemed unwise to separate adhesions, behind which, it is believed, an angioma is present. Six months after the boy's discharge from hospital he was stated to be well.

Figure IV
Case VII : left carotid angiogram : antero-posterior view

Case VII.—E.M.C., a housewife, aged thirty-one years, was examined on December 20, 1951. She had suffered epileptiform convulsions for sixteen years. One brother was in a mental hospital. One child was said to have died of fits at the age of four months. Her Fallopian tubes had been ligated a few months before she was examined, as her fits were worse during a pregnancy.

In 1935, when fifteen years old, she had had her first fit. She suddenly felt stiffness and numbness in the right hand, next in the right foot, and then in the right side of her face, and about ten minutes later she became unconscious. She had no idea what happened while she was unconscious, and her family would not tell her. Apparently clonic movements would occur on the right side, only very occasionally becoming generalized. She felt well on recovering consciousness, although a little dazed. She sometimes passed urine during a fit. The fits occurred at first every three or four months and later fairly regularly at about the time of each menstrual period, either at the beginning or at the end. However, attacks between the menstrual periods were not infrequent. During her last pregnancy they were more frequent. She might have three or four in one month. The fits had always been right-sided, except on one occasion, when she had exactly the same warning symptoms on the left side. The warning

period often amounted to ten or fifteen minutes, and would enable her to do several things before she lost consciousness. For example, she could remove her false teeth, get herself a cup of water and drink it and then go to bed. She had never been troubled by headache and had no complaint about her general health. Her last fit had occurred five to six weeks before she was examined at the Royal Perth Hospital. She then had six in succession. Recent medication had been the administration of 65 milligrammes of phenobarbital at night, 0·1 gramme of "dilantin" three times a day, and a bromide mixture. She was left-handed.

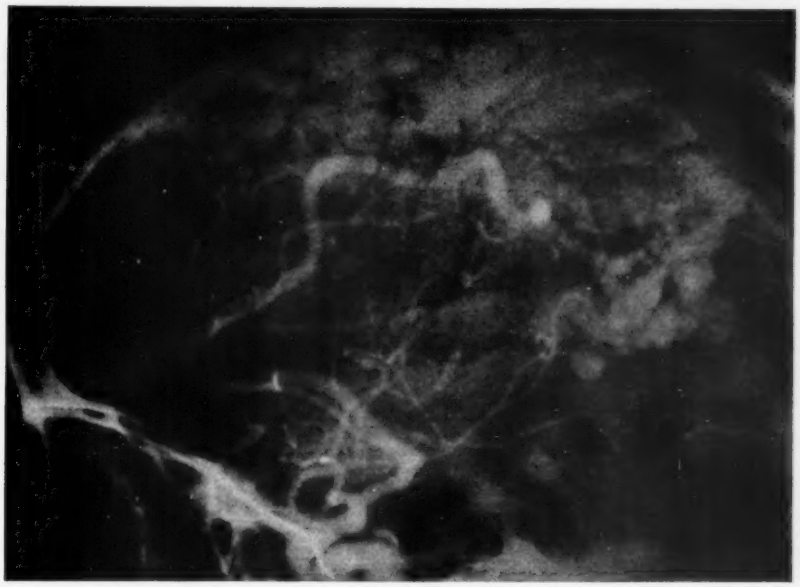

FIGURE V
Case VII: left carotid angiogram: lateral view

The patient was a well-built, healthy-looking woman of average intelligence. The systolic and diastolic blood pressures were 130 and 75 millimetres of mercury respectively. The skin, heart, lungs and abdomen were normal. The ocular fundi, pupils and cranial nerves and visual fields were normal. In the motor system, tone, power and coordination were normal. There was no impairment of the sensations of light touch, temperature or pin-prick. Joint and vibration senses were normal. The tendon and superficial abdominal reflexes were normal and equal. The plantar reflexes were flexor in type on both sides. The Wassermann and Kahn tests yielded negative results. A plain X-ray film of the skull showed no significant abnormality.

Left and right carotid angiograms were taken. The radiologist reported that the films showed a very large arterio-venous aneurysm in the left posterior parietal region, fed by the supracallosal branch of the anterior cerebral artery. The middle cerebral vessels were reasonably well filled and appeared to be normal, in that there was no displacement, and one did not have the impression that they entered the angioma (Figures IV and V). The right angiogram showed no communication between the right internal carotid system and the angioma on the left side. The presenting portion of the angioma appeared to be on the medial surface of the lobe.

Mr. Ainslie considered that it was scarcely possible to remove this angioma, and a less complete operation was felt to be unjustified. Fits had so far been the only symptoms, and it was thought it might be possible to achieve even better control of these by medical means. Close observation was recommended. The X-ray films and history were sent to Dr. Gosta Norlén, of Stockholm. He considered that the angioma was operable and that operation was indicated. However, he stated that none of the angiomata he had removed had been of such a large size.

On March 28, 1952, the patient reported that she had still had three to four fits a month. She was advised to reduce her salt and fluid intake before a menstrual period was due.

On May 30, 1952, she reported that she had had no fits but was having almost continuous headache. It was found that she was very worried about her son, who was a difficult child. It was considered that the headache was probably due to this, rather than to her obvious neurological lesion. She had been emphatic before that she had not suffered from headache.

CASE VIII.—P.B.H., a housewife, aged twenty-four years, was first examined in consultation at a private hospital on November 17, 1952. At the age of eight years she had become paralysed in the left arm and leg. This paralysis lasted about three weeks, and she then recovered. Ever since then she had periodically noticed numbness in the left thumb and forefinger, but only for a few seconds each time. There ha

occasionally been some clumsiness with finer movements of the left hand. Otherwise no disability had followed the paralysis until two years before she was examined. She then had a generalized epileptic fit in which she bit her tongue. One year later she had a similar fit, witnessed by her husband, when she was in bed. Six months later she began to have Jacksonian fits. There were a number of these, in which she had twitching of the left hand without loss of consciousness. Since that time she had had three, which were followed by a generalized fit and loss of consciousness for one to one and a half hours. The last one had occurred two weeks before she was examined. The left hand would go into painful flexion and the arm was forced behind her back. She could remember this before she lost consciousness. She had had recurrent headaches since the first fit two years before, but simple analgesics usually relieved them. At the time of the consultation she was four and a half months pregnant. Her first pregnancy had resulted in a miscarriage. She had recently been treated for pyelitis. Full general examination revealed no abnormality. The systolic and diastolic blood pressures were 110 and 70 millimetres of mercury respectively. The urine contained a faint trace of albumin, but culture had ceased to result in a growth of microorganisms. Neurological signs were confined to the sensory system. There was a slight defect in two-point discrimination in the left forefinger and thumb, and in the sense of position of the left great toe. The stereognostic sense was normal.

The cerebro-spinal fluid pressure at lumbar puncture was 230 millimetres of water. All constituents were normal. A plain X-ray film fo the skull was of normal appearance. On November 21 a right carotid angiogram taken at the neurosurgical unit at the Royal Perth Hospital revealed a very large angioma supplied by the right middle and anterior cerebral arteries. A huge exit vein drained into the superior sagittal sinus.

In view of the increasingly severe symptoms and her previous hemiplegia, operation after the birth of her baby was advised. A Cæsarean section has been recommended.

Summary

Cerebral angiomatous malformations have been found with increasing frequency since the introduction of cerebral angiography. Olivecrona found 83 cases among 3500 cases of cerebral tumour. The case histories of eight such patients are described.

The condition is a vascular maldevelopment, in which a tangled mass of undifferentiated vessels is interposed between arteries and veins. It is not a new growth.

The onset of symptoms often occurs in the second or third decade, and epilepsy and intracranial hæmorrhage are the commonest manifestations. Headache may or may not occur.

Operative removal planned with the aid of cerebral angiograms may result in complete cure.

Acknowledgements

Investigations upon these patients could not, of course, have been carried out without the expert help of colleagues in the unit. Mr. J. P. Ainslie founded it some three years ago. He performed all the operations. To him and to the following, active in the fields mentioned, my thanks are due: Dr. Ernest Beech (neurology), Dr. Ernest Green (oto-rhino-laryngology), Dr. T. R. Lubbe (pathology), Professor Ida Mann (ophthalmology), Dr. Arthur Merritt (radiology, including angiography), Mr. Ross Robinson (neurosurgery and angiography), and Dr. M. Sadka, registrar.

The first patient was referred to me by Dr. D. McPherson of Collie; the sixth and eighth were examined in consultation with Dr. V. H. Cooper and Dr. R. L. Leedman of Perth, respectively. The second and fifth patients were admitted to my ward at Royal Perth Hospital. The fourth patient was under the care of Dr. Cyril Fortune, and the third and seventh patients were under the care of Dr. Ernest Beech. To these gentlemen also my thanks are due. Upon reference to the unit, the patients were examined by all the members together.

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ON THE CLINICAL DETECTION OF ENLARGEMENT OF THE SPLEEN[1]

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A SPLEEN that is palpable below the left costal margin is almost always an enlarged spleen. Exceptions to this are rare and result from displacement or from abnormal mobility. The importance of detecting the presence of an enlarged spleen needs no emphasis; indeed, it was a sign familiar to the ancient physicians.

Texts on physical examination of the patient commonly include statements that a spleen that is palpable on abdominal examination is "considerably" enlarged (Chamberlain, 1943; Lambie and Armytage, 1947). Boyd (1950) states that the spleen is not likely to be palpable until it is about three times the normal size.

It is commonly taught that the palpable spleen is twice or thrice its normal size. This teaching implies that detectable splenomegaly is a late sign, and thereby lessens the importance attached to it. It is difficult to determine precisely what is meant by the size of the spleen, but it is assumed that size refers to volume rather than to surface dimensions.

Repeated examination of subjects with experimentally induced mosquito transmitted malaria led to a disbelief in this teaching, and an attempt was made to clarify the relationship between the palpability of a spleen and its actual size. Measurements of the shadow cast by the spleen on X-ray films were correlated with the clinical findings. Data are presented which are considered to indicate that a relatively small increase in the size of the spleen can be detected by simple abdominal palpation.

MATERIAL AND METHODS

The subjects were all soldiers who volunteered for chemotherapeutic trials in the L.H.Q. Medical Research Unit, Cairns, in 1945. All were initially free from systemic or local disease and were physically fit. Abdominal palpation was carried out by an examiner, who was seated on the bed near the subject's right hip. The right hand was used for palpation of the region of the left costal margin, and no attempt was made to perform bimanual examinations.

All the clinical data discussed in this paper were recorded by a single examiner, and the measurements refer to the distance (in centimetres) that the spleen could be felt below the left costal margin at full inspiration.

Immediately after the clinical examination, an X-ray picture of the spleen was made by means of the technique of Shepherd (1944). The length (L) and breadth (B) of the shadow of the spleen were measured on the X-ray film and rechecked later by a single examiner (Dr. J. H. Byrne), who had no knowledge of the clinical findings.

Fifty-eight sets of measurements were made on 46 subjects during the course of induced malaria.

The spleen is regarded as an irregular section of a prolate spheroid, and the volume is calculated by the use of the following formula:

$$\text{Volume} = K\frac{4\pi}{3}LB^2,$$

where L is the length and B the breadth as measured on the X-ray film, and K the fraction of the spheroid represented by the spleen. As this communication is concerned with relative changes in size, and as absolute values are indeterminable from the data, $K\frac{4\pi}{3}$ has been ignored. The "volumes" recorded are calculated directly from LB^2 and expressed in cubic centimetres.

RESULTS

The mean X-ray measurements of 15 subjects whose spleens were palpable, but not more than two centimetres below the costal margin, were compared with the mean measurements of 20 subjects with impalpable spleens (Table I). The latter group was equally composed of normal subjects and of subjects who may have been exposed to malaria but who never had evidence of infection. There was no significant difference between the mean spleen size of the normal subjects and of those with impalpable spleens. However, the mean diameters of the

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spleen shadows of the subjects with palpable spleens were 20% to 22% greater than the controls, and the calculated mean volume was 75% greater.

As the groups referred to in Table I consisted of different individuals, serial measurements were made on five subjects as set out in Table II. Subjects I to IV had their first X-ray pictures made prior to exposure to malaria and were

DISCUSSION

Validity of Measurements

Personal factors were excluded as far as possible by one observer making the clinical examinations and another the X-ray measurements. The results of the examinations were not communicated from one to the other until all measurements were completed.

TABLE I

Relationship of X-Ray Measurements of the Spleen to the Clinical Findings

Number of Subjects	Clinical Size: Centimetres Below Left Costal Margin	X-Ray Film Measurements				
		Length × Breadth (Centimetres)	"Volume" (Cubic Centimetres)	Percentage Difference		
				Length	Breadth	"Volume"
10	Impalpable (normal)	14·7×7·6	870			
10	Impalpable	14·1×7·5	810			
15	1–2	17·5×9·0	1418	22	20	75

TABLE II

Relationship of X-Ray Measurements of the Spleen to the Clinical Findings in Five Subjects During the Course of Induced Malaria

Subject Number	Clinical Size of Spleen: Centimetres Below Left Costal Margin	X-Ray Film Measurements				
		Length × Breadth (Centimetres)	"Volume" (Cubic Centimetres)	Percentage Difference		
				Length	Breadth	"Volume"
I	(*a*) Impalpable (normal) ..	15·0× 7·0	735			
	(*b*) Less than 1 to 2	16·0× 8·0	1024	7	14	39
II	(*a*) Impalpable (normal) ..	15·0× 9·0	1215			
	(*b*) 2	16·0×10·0	1600	7	11	32
III	(*a*) Impalpable (normal) ..	16·0× 8·0	1024			
	(*b*) 4	20·5× 9·5	1850	28	19	81
IV	(*a*) Impalpable (normal) ..	15·0× 7·0	735			
	(*b*) 6	20·5× 9·0	1661	37	29	126
V	(*a*) 2	15·0× 9·0	1215	25	50	181
	(*b*) 4	17·0× 9·5	1534	42	58	255
	(*c*) 5	18·0×10·0	1800	50	67	317
	(*d*) 4	17·0× 9·5	1534	42	58	255
	(*e*) Impalpable	12·0× 6·0	432			

normal. At the time of the second X-ray examination Subjects I and II had palpable spleens, but the measured diameters had increased by only 7% to 14%, and the increase in calculated "volume" was only 32% to 39%. Increases of 81% to 126% in spleen volume were recognized clinically in the third and fourth subjects as a change from normal, with impalpable spleens, to grossly abnormal with spleens palpable four and six centimetres respectively below the left costal margin. The fifth subject was not measured by X-ray examination prior to exposure to malaria, but the change in clinical findings from splenomegaly of two centimetres below the costal margin to "impalpable spleen" represented a change of 181% in calculated spleen "volume".

The ratio $L : B$ was calculated from the X-ray measurement made on three groups of patients with spleens of different clinical sizes, and it was found to be constant. The mean volumes were found to be the same (20 subjects with impalpable spleens, mean $L : B = 1{\cdot}933$, $\sigma = 0{\cdot}198$; 20 subjects with spleens palpable up to three centimetres below the costal margin, mean $L : B = 1{\cdot}963$, $\sigma = 0{\cdot}244$; 18 subjects with spleens palpable from four to seven centimetres below the costal margin, mean $L : B = 1{\cdot}938$, $\sigma = 0{\cdot}198$). This indicated that comparable projections of the spleen on the X-ray film were obtained throughout the series. It also indicated that the spleen, as measured, enlarged in a regular manner. It is apparent that if $L : B$ is constant the percentage change

in calculated volume will not differ significantly if one considers the spleen to be an oblate spheroid ($V=L^2B$) rather than a prolate spheroid ($V=LB^2$).

Observations on subject V over a considerable period of time showed that the X-ray measurements were reproducible.

Significance of Findings

The average difference between the calculated volume of the spleens of normal subjects and of subjects with definite clinical splenomegaly was 75%. However, serial readings on a few subjects revealed that one observer, at least, could palpate a spleen that had increased in volume by only 39%. These findings were confirmed by finding increases in volume of about 100% when an impalpable spleen became palpable four to six centimetres below the left costal margin.

It is apparent that relatively small increases in spleen volume were detected by simple abdominal palpation. The enlargement was no more gross than the first clinically detectable cardiac, uterine or lymph gland enlargement.

The ease with which the spleen can be palpated depends not only on its size, its consistency and its displacement in respiration by the diaphragm, but also upon the state of the abdominal wall. The difficulties associated with obese subjects and with women who have poor diaphragmatic movement are well recognized. A lax abdominal wall assists in the detection of small degrees of splenomegaly. The subjects reported here were all physically fit, and none were significantly obese; the development of the abdominal musculature was better than that usually seen in the average patient. There appear to be no grounds for assuming that the circumstances were unusually favourable for palpating the spleen in this group of subjects.

It is pertinent to consider the origin of the general teaching that detectable splenomegaly indicates gross splenomegaly, that the palpable spleen is twice to thrice the size of the normal spleen. Apart from radiological measurement with or without the use of contrast techniques, there seem to be two sources of information, the autopsy room and the operating theatre.

Experiments based on autopsy findings are open to criticism, for it is well recognized that the spleen contracts in the agonal state. The wrinkled capsule is a familiar post-mortem finding. The spleen which is diseased would not be expected to contract to the same degree as the normal spleen. A similar criticism may be directed against the findings at laparotomy—it is many years since Barcroft demonstrated the considerable contraction of the spleen during stress in the normal animal.

It is of interest to note that the mean X-ray dimensions of the normal spleens recorded here—14·7 by 7·6 centimetres—are similar to those recorded in anatomical texts—12 or 13 by 7·0 or 7·5 centimetres (Miller, 1938; "Gray's Anatomy", 1946). Shepherd (1944) made comparable observations on subjects similar to those reported here, though he drew different conclusions: "Palpation of the spleen, except in cases of marked enlargement, would appear to be an unreliable sign".

It is contended that careful palpation of the spleen will reveal splenomegaly of relatively small magnitude. The teaching that the palpable spleen is grossly enlarged should be abandoned, for it is incorrect and it diminishes the importance of an easily elicited clinical sign.

SUMMARY

1. The size of the spleen in normal subjects and in subjects with malaria has been estimated by abdominal palpation and by the measurement of shadows cast by X rays.

2. Correlation of clinical and X-ray measurements revealed that a spleen that had increased in calculated volume by 40%, corresponding to an increase in apparent length and breadth of less than 15%, was palpable below the left costal margin.

3. The teaching that the palpable spleen is twice or thrice its normal size is incorrect.

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THROMBOSIS AND EMBOLISM IN CHRONIC RHEUMATIC ENDOCARDITIS[1]

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CHRONIC rheumatic endocarditis has been encountered at autopsy in 137 instances in the last fifteen years at the Royal Prince Alfred Hospital. In all except 12, death was due to cardiac failure or to some complication such as subacute bacterial endocarditis or massive infarction of organs.

The age at death and the sex distribution are shown in Table I. As autopsies can be performed only with the permission of the relatives of deceased persons, the figures do not give the true sex incidence, women being far readier to grant permission for autopsy than men. It can be seen that nine-tenths of all patients were dead by the sixtieth year.

TABLE I
Age at Death of 137 Patients with Chronic Rheumatic Carditis

Age (Years)	Males	Females
10 to 20	9	3
21 to 30	9	10
31 to 40	12	8
41 to 50	17	16
51 to 60	19	21
61 to 70	3	7
71 to 80	1	2
Totals ..	70	67

The valvular involvement was as follows: mitral valve alone 90 cases, mitral and aortic valves 36 cases, mitral, aortic and tricuspid valves six cases, mitral and tricuspid valves three cases, mitral, aortic, tricuspid and pulmonary valves one case, aortic valve alone one case.

As mitral valve involvement was the commonest and most serious lesion, this has been graded according to the size of the valvular orifice (Table II). Auricular fibrillation occurred more frequently in patients with severe mitral stenosis than in the less severely affected. There were 47 cases (34%) in which auricular fibrillation had occurred. The incidence according to the size of the mitral orifice can be seen in Table II.

TABLE II
Showing the Severity of Stenosis and its Relation to Auricular Fibrillation

Size of Mitral Orifice	Number of Cases	Previous Auricular Fibrillation
Grade I: Mitral valve admitting more than little finger ..	62	12
Grade II: Mitral valve admitting little finger only	32	11
Grade III: Mitral valve admitting tip of little finger	30	16
Grade IV: Mitral valve not admitting tip of little finger ..	13	8
Total	137	47

SUBACUTE BACTERIAL ENDOCARDITIS

Subacute bacterial endocarditis was present in 29 cases. In six, the predominant lesion was stenosis of the mitral valve, but in the remainder incompetence predominated.

INFARCTS

Infarctions occurred in 76 cases. Of the 108 cases without subacute bacterial endocarditis, in 58 (54%) there were infarcts, of which 43 (40%) were pulmonary. In 18 of the 29 cases of subacute bacterial endocarditis infarcts were found, only four of which were pulmonary.

TABLE III

Grade	Number of Subjects	Number of Subjects with Pulmonary Infarcts
I.	62	12
II.	32	13
III.	30	16
IV.	13	6

The incidence of pulmonary infarcts in all groups can be seen in Table III. Infarctions of the lung were less frequent in the group with

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mitral incompetence. This accounts for the lower incidence in subacute bacterial endocarditis, as incompetence was the predominant lesion in that group.

Infarctions were found much more frequently in patients who had had auricular fibrillation than in those who had had regular rhythm. This applied both to pulmonary and to systemic infarcts. Of the 108 patients in whom there was no superadded bacterial endocarditis, 44 had had auricular fibrillation. Table IV sets out the incidence of infarctions in these cases.

TABLE IV

Observation	Auricular Fibrillation	Regular Rhythm
Number of subjects without subacute bacterial endocarditis	44	64
Pulmonary infarctions ..	16	13
Pulmonary and systemic infarctions	8	6
Systemic infarctions ..	7	7

ARTERIAL THROMBOSIS

Arterial thrombosis was the cause of infarction in a large number of cases. There were 28 examples of gross arterial thrombosis, and in addition eight examples of thrombosis were observed in small branches of the pulmonary arteries and were confirmed by microscopic examination. Microscopic thromboses were not sought as a routine procedure, and these eight cases do not represent the true incidence.

The sites of massive arterial thrombosis were as follows: massive pulmonary artery thrombosis, 14 cases; massive pulmonary artery thrombosis and thrombosis of other arteries (internal carotid in one case and both coronary arteries in the other), two cases; thrombosis of the abdominal aorta, one case; thrombosis of the abdominal aorta and of the superior mesenteric and splenic arteries, one case; superior mesenteric artery thrombosis (subacute bacterial endocarditis in one case), three cases; thrombosis of the common iliac artery, two cases; thrombosis of the basilar artery (subacute bacterial endocarditis in one case), four cases; thrombosis of the coronary artery, one case. The total number of subjects with gross thrombosis was 28; the number of subjects with thrombosis of small pulmonary arteries was eight.

The number of subjects with arterial thrombosis is not sufficient for statistical analysis, but there were more examples amongst those in which mitral stenosis was the predominant lesion.

From the figures in the tables it can be seen that infarctions of various types are very common in chronic rheumatic endocarditis. A feature of interest is the unusually large number of subjects with arterial thrombosis, particularly pulmonary artery thrombosis. Massive pulmonary thrombosis was often bilateral, and in some cases every large pulmonic branch appeared to be occupied by a pale adherent thrombus, the free rounded end of which just projected into the main pulmonary artery of its particular side. It occurred more frequently in association with auricular fibrillation than with normal rhythm. In some cases in which there was a history of repeated infarctions, organized thrombus was demonstrable.

The cause of the thrombosis was not always apparent. In most cases there had been accompanying femoral or saphenous phlebothrombosis of more recent origin. However, in one case it was possible to demonstrate curled and twisted emboli, to which thrombus had been added in the pulmonary arteries. In another case there was an obvious pulmonary embolus from the femoral veins. In most, this embolic basis was not demonstrable, although it was not always excluded. Thrombi in the right side of the heart, though less common than in the left side, were also occasionally found. In the arteries of the pulmonary circulation in these cases of pulmonary thrombosis atheroma was almost always present, though of much less degree than that seen in the systemic circulation of the average elderly person who comes to autopsy.

Thrombosis of the abdominal aorta, in each case, commenced on an atheromatous plaque, which had no superficial ulceration, and which under ordinary circumstances, would not have been the site of thrombus formation.

In the case of thrombosis of the internal carotid artery, a plaque of intimal fibrosis with some calcification of the media was the starting point of the thrombus.

Thrombosis of the basilar artery occurred in four cases. In one subacute bacterial endocarditis was present, and in another there was thrombus in the left atrium. In these two cases, small emboli may have lodged in the basilar artery and caused thrombosis there. In one of the other two cases there was minimal atheroma, and in the remaining case the artery appeared healthy both to the naked eye and under the microscope. No source of embolism was found in this case.

Intravascular thrombosis depends upon three factors—namely, the state of the vessel wall,

the rate of flow and the coagulability of the blood. The pulmonary arteries in mitral stenosis were usually affected by some degree of atheroma, and in some cases heart failure may have slowed the blood flow. However, there were others in which heart failure occurred only after the appearance of infarction. Hence it is logical to suppose that there was increased blood coagulability in those cases, as the atheroma was not severe by the standards used in the examination of systemic vessels. In other forms of cardiac disease pulmonary infarctions and massive arterial thromboses are less common than in this series. This suggests that chronic rheumatic endocarditis is a predisposing cause of thrombus formation.

The incidence of venous thrombosis is not determinable. Although a large number of venous thrombi were found at autopsy, in many of the series the state of the peripheral veins has not been recorded.

ARTERITIS

Acute arteritis of pulmonary vessels was observed on seven occasions. In one case the mitral valvular orifice admitted the passage of the little finger, but in all the others no more than the tip of the little finger could be inserted. The heart was grossly hypertrophied in each case, the smallest weighing 430 grammes and the largest 870 grammes.

The lesion was of necrotizing type, and it involved small arteries, the muscle coat being chiefly affected in the earliest lesions. The necrosis usually occupied a segment of the arterial wall, but in some cases it completely encircled the vessel. Thrombosis supervening upon arteritis has seldom been observed. Healing appeared to occur fairly rapidly, accompanied by proliferation of intimal connective tissue with consequent reduction in the size of the lumen. In some cases intimal proliferation and necrosis could be seen side by side in the same vessel.

The occurrence of pulmonary arteritis parallels that observed in systemic hypertension. Very high pressure may cause necrosis of small arteries and arterioles. In all the subjects exhibiting this reaction there was evidence of severe pulmonary hypertension, though no measurements had been made during life.

Acute interstitial pneumonia was always related to the arteritis.

SUMMARY

A series of 137 autopsies in consecutive cases of chronic rheumatic endocarditis has been analysed, and the incidence of infarctions, particularly pulmonary infarction, has been discussed. It has been found that patients suffering from mitral stenosis of rheumatic origin are particularly prone to develop infarctions which in many cases are due to arterial thrombosis. The incidence is higher in the presence of auricular fibrillation.

MELORHEOSTOSIS : ITS RELATION TO ASSOCIATED CONDITIONS AND A CASE REPORT [1]

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The name melorheostosis was introduced by Léri and Joanny (1922). In their patient, a woman, aged thirty-nine years, there was throughout the whole length of the left upper extremity a most singular bony hypertrophy, not affecting the whole of this or that bone, but certain bones and certain parts of bones.

Many cases of melorheostosis have now been recorded, and some of these have been associated with a variety of other pathological conditions. These associations at first sight may be regarded as fortuitous, but we suggest that these apparently unrelated conditions have a common background, and are predisposed to by intrinsic factors which influence growth and development.

We shall first give an account of a patient who has been under observation for many years; the clinical manifestations, the radiological features and the histo-pathological evidence together present a picture distinctive of melorheostosis.

Report of a Case

The patient, a man, aged forty-six years (in 1951), was for many years under the care of the late Dr. A. Aspinall; he was born in Birmingham, England, and in early adult life was a plasterer by occupation. There was nothing of note in the family history or personal history except that he had suffered from asthma since the age of eight years. Asthma is recorded as being severe in the 1930 and 1932 hospital records. In Figure I it is evident that the affected right leg is longer and larger than the normal left leg. This photograph was taken in 1936. At the age of seven years a slight protuberance was noticed on the anterior aspect of the right tibia, at the age of eight or nine years slight bowing of the right tibia, at the age of ten years slight bony enlargement in the region of the right ankle and right knee; the right femur was apparently irregular in outline at the age of sixteen years. During this period he played games and led an active life.

At the age of twenty years the patient noticed that on taking severe exercise he felt in the right leg a burning sensation of indefinite radiation.

Figure I.
The affected right leg is longer and larger than the left (photograph taken in 1936).

From the age of twenty years onwards the bones of the right lower extremity showed a progressive irregular increase in their transverse measurements, and loose hard nodules became palpable in the muscles of the right thigh. These nodules were 2·5 to 5·0 centimetres in diameter.

When the patient was aged twenty-three years a small cutaneous ulcer appeared on the medial aspect of the lower third of the right leg; the ulcer responded quickly to local treatment.

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From the age of twenty-four years onwards the patient suffered from severe pain localized to the right hip joint, and again of indefinite radiation in the right lower limb. Attacks of

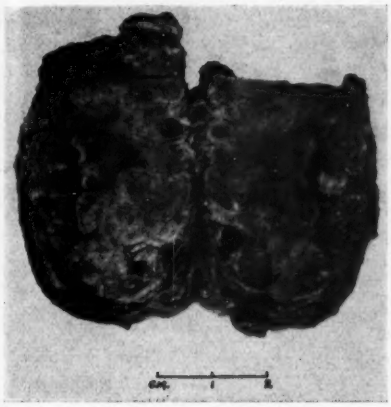

FIGURE II.
Bony tumour removed from soft tissues near right ilium. (see Figure III) in 1934.

pain were of sudden onset, unrelated to physical exertion or stress, and lasted for twenty-four to thirty-six hours. These attacks occurred at

FIGURE III.
There is extensive sclerosis of the right half of the pelvis and right femur. A large "osteoma" is situated in the right ischial and pubic regions, a smaller "osteoma" in the soft tissues near the right ilium. The skiagram was taken in 1934. (By courtesy of *The British Journal of Radiology* and Dr. H. R. Sear.)

intervals of about six months; they were accompanied by severe attacks of sweating and by fever of moderate degree, the usual temperature ranging from 37·8° to 38·3° C. An indication of the severity of the pain was given by the slightness of the response to opiates and potassium iodide.

From the age of thirty-eight years onwards he continued to suffer from severe bouts of pain localized to the pelvis and lumbar region, but these bouts were unaccompanied by fever. The nodules appeared harder and larger and firmly attached to the underlying bone. Joint movements of the affected limb had gradually diminished to about 60% of the normal range.

FIGURE IV.
In parts of the bones of the right inferior extremity dense sclerosis is apparent.

At the age of forty-three years flexion of the joints was approximately 25% of normal in the right hip, 30% of normal in the right knee and nil in the right ankle. Recurrent ulceration had been noted in the lower third of the right limb during this period.

When interviewed on April 4, 1950 (at the age of forty-five years), the patient said that the pain had changed its character. He complained of severe cramping pain of sciatic distribution, and pain of a deep burning, boring character, relatively constant, and causing him to lie "rigid". This pain was said to be present in the lower lumbar area of the back

and in the right gluteal region. Such pain occurred in attacks at intervals of five to six weeks, and lasted forty-eight to seventy-two hours. During an attack he lay in the position of opisthotonos. The pain was relieved only

FIGURE V.
In parts of the bones of the right inferior extremity dense sclerosis is apparent.

by opiates. He considered that trauma or undue exertion might precipitate attacks, but he also noticed that these bouts of pain were often spontaneous in onset.

Physical examination on that date disclosed the patient to be of good physique and well-nourished. The right lower limb was semi-flexed. A large nodule was palpable in the right buttock, a smaller one in the hind part of the right thigh; hard nodules could also be felt in the outer part of the right thigh, smaller nodules in the right quadriceps and several in the right leg. The right tibia was bowed in a forward and outward direction, and the bone was unduly prominent; the right heel was also prominent. The right foot was broader and longer than the left, the increase in size being due to the bony enlargement of the tarsus and metatarsus. The right second toe was longer than the left and was increased in breadth; the increase in size was due to bony enlargement of the phalanges. The muscles of the right thigh and buttock were wasted and appeared hard in consistency; the right quadriceps on palpation seemed to be composed of firm fixed hard tissue. The leg muscles were wasted.

Signs of previous ulceration were evident on the medial and lateral aspects of the lower third of the right leg. The skin of the right foot was tense, inelastic and mottled. The right limb was warmer than the left, and the bone was of irregular contour and irregularly thickened.

The range of movements of the joints was estimated to be as follows: hip, nil; knee, 15°; ankle, nil. Sensation was normal in the right

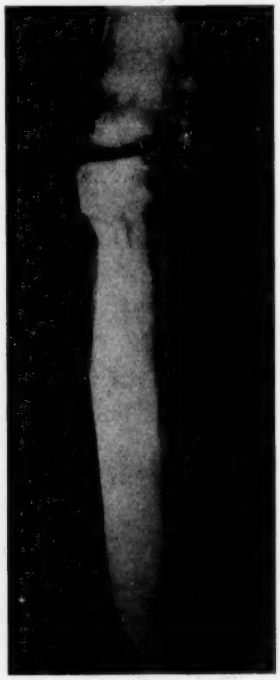

FIGURE VI.
In parts of the bones of the right inferior extremity dense sclerosis is apparent.

lower extremity, but all reflexes were absent. His blood pressure was 150 millimetres of mercury, systolic, and 90 millimetres, diastolic, and there was slight albuminuria. The blood count was essentially normal; the serum inorganic phosphorus content was 2·7 milligrammes per 100 millilitres; the alkaline phosphatase content (test repeated) was within

normal limits. The Wassermann test had been found to produce a negative result in 1930.

After this examination the second right toe was amputated, as it interfered with the wearing of shoes. The patient has continued to experience bouts of pain, but has maintained his present occupation as a traveller.

At X-ray examination in 1930 the condition was regarded as "marble bone disease" affecting the right side of the pelvis, and the right femur, tibia and foot. At this stage ossification was observed in muscles about the pelvis—namely, the glutei and adductors. In 1932 the diagnosis of melorheostosis was made by Dr. K. B. Voss.

The radiological appearances are to be seen in Figures III to VII. These skiagrams were taken between the years 1934 and 1938 inclusive. Figure III corresponds with Figure II in the paper by Sear (1947) on "melorheostosis and the creeping periostitic form of leontiasis".

In Figure III (1934) it is evident that very dense areas of bone are extensively distributed throughout the right innominate bone and the right femur, that a large bony tumour is present in the region of the right ischium and pubis, that a smaller one is present in the soft tissues near the right ilium, and that the bone dystrophy is limited to the right half of the pelvis and the right femur.

In Figures IV to VII inclusive (1934 to 1938) it is clear that the sclerotic process evident in

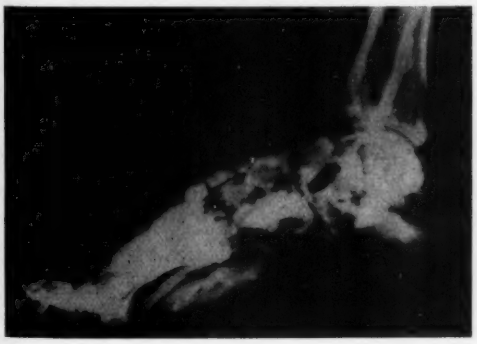

FIGURE VII.
In parts of the bones of the right foot dense sclerosis is visible.

the right side of the pelvis and the upper part of the right femur (Figure III) extends throughout the whole length of the right inferior extremity. The sclerosis of the bones of this extremity is not complete; longitudinal lines of separation divide the involved from the relatively uninvolved portions of the affected long bones; this applies particularly to the tibia. Though the bones of the foot are densely sclerotic for the most part, portions of some bones, especially the calcaneum, show little or no sclerosis.

Pathological Findings

In 1934 an oval encapsulated bony tumour, which was attached to the posterior surface of

FIGURE VIII.
Showing the structure of the bony tumour of the right fifth metatarsal bone. ×4·75.)

the right *tensor fasciæ latæ*, was removed surgically. This tumour (Specimen 1) is to be seen near the right ilium in Figure III and its gross appearances after removal and bisection are to be seen in Figure II. At the same time the proximal phalanx of the right fifth toe with bony tumour attached to its under surface was removed (Specimen 2); the distal phalanx of this toe was removed some years earlier.

Specimen 1 (Figure II) weighed 46 grammes and measured 5·0 centimetres by 3·2 centimetres by 2·8 centimetres. On section it seemed to consist essentially of a mass of very dense bone surrounded by adipose tissue. In the adipose tissue there was a small portion of dense bone quite separate from the main mass. Specimen 2 weighed 14 grammes. On section it was seen to be composed chiefly of compact bone in two separate portions. The bone was covered by a layer of fibrous tissue and adipose tissue.

Histological examination of the sections of Specimen 1 show compact bone differing only

slightly in structure from normal compact bone. In portions of the specimen cartilaginous-looking tissue is to be seen; this merges insensibly in the more bony parts of the preparation. The spaces between the trabeculæ of

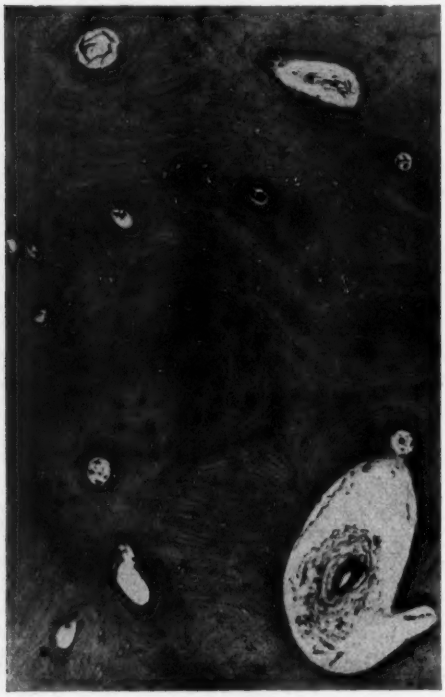

FIGURE IX.
Dense portion of Figure VIII under higher magnification. (×75.)

bone contain loose connective tissue in which engorged blood vessels are conspicuous. In some of the intertrabecular spaces the tissue is fibro-cellular; in them the fibro-cellular tissue tends to merge insensibly in the surrounding solid tissue which is cartilaginous, the cartilage itself gradually merging in the bone.

In 1950 the enlarged right second toe was removed. Portion of the right fifth metatarsal bone, with tumour attached to the plantar surface of its head, was also removed. The toe measured 6·5 centimetres in length and 6·5 centimetres in circumference; the joints could not be moved. This toe was not examined microscopically. The mass of bone from the right fifth metatarsal bone weighed 26 grammes and inspection of the cut surface revealed ivory bone. A section through the whole of this specimen is shown in Figure VIII. Most of the tissue is very dense bone, and even in the trabeculated portions the trabeculæ are dense. Figure IX shows the structure of the dense bone; Haversian canals, many of them very small, and Haversian lamellæ are to be seen in it; the bone cells appear as small points.

Figure X shows portion of the trabeculated bone; the bony trabeculæ are dense and the intertrabecular spaces are here occupied by rather loose connective tissue with occasional blood vessels in some.

In Figure XI cartilaginous tissue can be seen merging insensibly in the bony tissue. Figure XI shows the structure of the bony tumour near its free surface (shown to the right of Figure VIII). Cartilage was found only fairly near the free surface. There was no continuous layer of

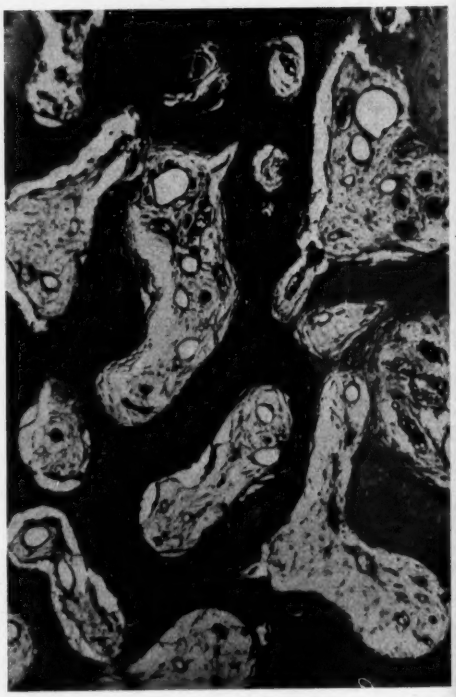

FIGURE X.
Trabeculated portion of Figure VIII under higher magnification. (×75.)

cartilage on the surface of the bony outgrowth such as one sees in osteochondromatous "exostoses", and in some situations the periosteum covering the free surface of the tumour lay against compact bone; in a few situations, however, the covering connective tissue layer lay directly against cartilaginous-looking tissue.

The changes just described as present in the tumour of the right fifth metatarsal bone correspond closely with those found in the tumour in the soft tissues near the right ilium (Figures II and III). Both of these lesions are looked on as essentially of the nature of osteomata.

DISCUSSION

In patients suffering from melorheostosis various other conditions have been found. These include (i) osteopœcilia (osteopoikilosis, *osteopathia condensans disseminata*), (ii) osteopetrosis (marble bones, Albers-Schönberg disease), (iii) fibrous dysplasia of bone, (iv) vascular malformations, (v) scleroderma, (vi) Meige's trophœdema (Milroy's disease), (vii) chondrodystrophy (achondroplasia), (viii) craniostenosis, (ix) neurofibromatosis, (x) tuberous sclerosis.

Osteopœcilia and Osteopetrosis

Phalen and Ghormley (1943) stated that osteopoikilosis, osteopetrosis and melorheostosis were three types of condensing or sclerosing osteopathy, and their case of *osteopathia condensans disseminata* associated with coarctation of the aorta presented radiological features of all three types of sclerosing osteopathy.

In three of the cases of osteopetrosis recorded by Higinbotham and Alexander (1941) syndactylism was present. Seigman and Kilby (1950) found hypoplasia of the terminal phalanges of the fingers and toes in a patient with osteopetrosis.

With regard to bony tumours in soft tissues, is melorheostosis related ætiologically to so-called *myositis ossificans progressiva*?

Bony tumours in soft tissues have been recorded in melorheostosis on several occasions. Léri and Lièvre (1928) made a histological examination of a bony mass in the opposite infraspinatus muscle of the patient in Léri's original Case I and found it to be composed of practically normal bone. Franklin and Matheson (1942) stated that apart from the bone changes in their case there were some very dense nodular deposits (see their Figure II) in the soft tissues of the affected right lower limb. In our case of melorheostosis "osteomata" in the soft tissues of the affected limb were a conspicuous feature. Wilson (1940) stated that *myositis ossificans* came on during the early months or years of life as a small swelling in muscle with pain, a little œdema and perhaps some fever; microdactyly (thumb or great toe) is a feature of two-thirds or more or all cases; syndactyly and other congenital anomalies have been reported. The possibility that melorheostosis is related ætiologically to *myositis ossificans progressiva* seems worth keeping in mind.

Fibrous Dysplasia of Bone

O'Connell (1951) described an interesting condition in a girl, aged eighteen years, under

FIGURE XI.

Portion near free surface of the tumour (upper right of Figure VIII) more highly magnified. Note cartilaginous-looking tissue merging in the bony tissue. (×75.)

the heading melorheostosis (Léri). Histological examination of the affected right tibia (O'Connell's Figure XII) showed trabeculæ of bone separated by cellular fibrous tissue. Dorothy Russell, who made the histological examination, said that the appearances were those of "a fibrous dysplasia of bone, with features suggestive both of Paget's *osteitis deformans* and of *osteitis fibrosa*". We suggest that in this patient the changes of both melorheostosis and fibrous dysplasia were present.

If one variety of sclerosing osteopathy—namely, *osteopathia condensans disseminata*—occurs in association with polyostotic fibrous

dysplasia of bone as in the patient described by Osgood (1946), it would not be surprising if another variety of sclerosing osteopathy—namely, melorheostosis—should occur in association with fibrous dysplasia of bone, as we suggest occurred in O'Connell's case. If our suggestion is valid, the possibility that fibrous dysplasia of bone and the sclerosing osteopathies have a common ætiological basis seems worthy of consideration.

Support is given to this notion by the occurrence in a patient with polyostotic fibrous dysplasia described by Jervis and Schein (1951) of cerebral changes somewhat similar to those found in tuberous sclerosis and in von Recklinghausen's neurofibromatosis, both of which conditions have been described in patients with melorheostosis, in tuberous sclerosis by Hall (1943) and in neurofibromatosis by McCarroll (1950).

Vascular Malformations

Murray (1951) described melorheostosis associated with congenital arterio-venous aneurysms.

Stauffer *et alii* (1941) recorded congenital arterio-venous aneurysms in a patient with polyostotic fibrous dysplasia with cutaneous pigmentation. Phalen and Ghormley (1943) found coarctation of the aorta in a patient with one of the sclerosing osteopathies—namely, *osteopathia condensans disseminata.*

Coleman (1938-1939) reported *osteitis fibrosa disseminata* (which we take to be polyostotic fibrous dysplasia) in a mentally dull boy with partial coarctation of the aorta and aneurysm of the thoracic aorta. Norman and Taylor (1940) described a congenital diverticulum of the heart (heterotopia of aortic tissue) in association with epiloia (tuberous sclerosis). Hall (1943) described tuberous sclerosis in a patient with melorheostosis.

Scleroderma

Scleroderma was found in association with melorheostosis by Dillehunt and Chuinard (1936), by Gillespie and Siegling (1938), by Hall (1943), and by Thompson *et alii* (1951).

Meige's Trophœdema (Milroy's Disease)

Meige's trophœdema was considered by Meisels (1929) to be present in a woman with melorheostosis described by him. Franklin and Matheson (1942) described a case of melorheostosis with great increase in size of the right lower limb associated with œdema. There had been recurrent ulceration of the dorsum of the right foot (melorheostosis affected the right leg). The nature of the œdema in this case is uncertain.

Bulloch (1909) said that some patients with trophœdema (chronic hereditary œdema), in addition to the chronic œdema, suffered from " acute attacks " ushered in with violent pain, shivering and rise in temperature. In our patient with melorheostosis, at one stage, bouts of pain were accompanied by rigors and pyrexia.

No satisfactory explanation for the fever in Meige's trophœdema is forthcoming, nor are we able to offer a satisfactory explanation for the pyrexial attacks in our patient with melorheostosis.

Chondrodystrophy (Achondroplasia)

Hilton (1934) reported the unusual association of multiple melorheostosis with familial chondrodystrophy in a girl, aged ten years. The patient's mother and two maternal aunts were similarly affected. Bloom (1933) stated that the case of osteopœcilia described by Guelliars and Mollaret (1930) occurred in an achondroplastic dwarf. Pines and Lederer (1947) stated that achondroplasia might be found in patients with osteopetrosis, but they gave no references.

Pritchard (1928) described a boy, aged three and a quarter years, with achondroplasia ; he was a twin ; his co-twin was a perfectly normal girl ; the father was extremely tall. As Pritchard states, such an instance (and others have been reported) seems to prove that achondroplasia cannot be caused by any endocrine defect or blood condition existing in the mother, for if this were the cause both twins would be similarly affected.

Achondroplasia frequently occurs in several generations. Hunter (1928) described it in three generations — grandfather, father, daughter.

Knaggs (1926) stated that Hektoen (1903) described a small, short-limbed dwarf, aged forty-five years, showing some of the features of *osteogenesis imperfecta* and certain appearances suggestive of achondroplasia. Writing of *osteogenesis imperfecta,* Fairbank (1948) stated that the relative shortness of the limbs in his Case I (Fairbank's Figure III) suggested achondroplasia, and that the bending of the tibia in his Case II was very like that often considered to be related to pseudarthrosis. Stalmann (1933) and others have recorded congenital pseudarthrosis of the tibia in neurofibromatous families. Fraser (1918-1919) and others have reported *fragilitas ossium* (*osteogenesis imperfecta*)

and otosclerosis occurring in the same individuals. Mayer (1923) found otosclerotic foci in some patients with congenital deaf-mutism. In a patient who was congenitally deaf, Inglis (1952) described widespread cutaneous lentigines. Ito *et alii* (1949) found cutaneous lentigines and small fourth metatarsal bones in a patient with abortive von Recklinghausen's disease.

McCarroll (1950) described von Recklinghausen's neurofibromatosis in patients with melorheostosis.

Léri and Linossier (1924) described two patients (mother and daughter) who had attenuated achondroplasia or hypochondroplasia. The daughter, aged twenty-one years, had notable shortening of the fourth finger on both sides. The feet showed deformities exactly similar to those of the hands. The mother (and her mother) showed analogous deformities. Radiographic examination confirmed the shortening of the fourth metacarpals and metatarsals.

Craniostenosis

Craniostenosis was found in a patient with melorheostosis by Putti (1927). Joske (1948) described, in a man, aged thirty-two years, and in his daughter, aged five years, a condition recognized by Lowe (1948) to be *dysostosis craniofacialis*. The man had eight brothers and one sister; two of the brothers were like twins, one was an achondroplastic dwarf.

Syndactyly has often been recorded in patients with cranio-facial dysostosis, as is evident from the table published by Brown and Harper (1946). It has also occurred in osteopetrosis (Higinbotham and Alexander, 1941).

Neurofibromatosis

McCarroll (1950) found unmistakable evidence of melorheostosis in two of his cases of neurofibromatosis. In our case of melorheostosis and in the case recorded by Franklin and Matheson (1942) there was increase in size of the affected limb. Local gigantism has been referred to by Inglis (1950*c*) as a manifestation of neurofibromatosis.

In Meisel's (1928, 1929) case of melorheostosis the limb was a little shortened. In the case of melorheostosis recorded by Thompson *et alii* (1951) there was one and a half inches of shortening of the femur, and one inch of shortening of the tibia. Jaffe (1945-1946) described two inches of shortening of the left tibia as compared with the right in a girl, aged eighteen years, with neurofibromatosis.

Inglis (1950*b*) considered small size of individual bones to link up with neurofibromatosis. In previous sections of this paper neurofibromatosis has been linked indirectly with other conditions which are sometimes associated with melorheostosis.

Tuberous Sclerosis

Hall (1943) described melorheostosis in a patient with tuberous sclerosis.

Inglis (1950*a*) recorded polycystic disease of the kidney in an infant with tuberous sclerosis of the brain. Urbach and Wiedman (1929) described Pringle's disease (so-called *adenoma sebaceum*—a component of the tuberous sclerosis complex) and von Recklinghausen's disease in a child, aged ten years. In view of the strong evidence that polycystic disease of the kidney (Cairns, 1924-1925) and cutaneous neurofibromata (Preiser and Davenport, 1918) are hereditary in man, Schlumberger's (1950) observation of polycystic kidneys and cutaneous neurofibromata both present in several goldfish in the one pond seems to indicate that faulty operation of fundamental biological laws of growth and development underlies these pathological conditions.

SUMMARY

Melorheostosis, one of the condensing or sclerosing osteopathies, is an uncommon dystrophy of bone which may be associated with osteopœcilia (osteopoikilosis, *osteopathia condensans disseminata*), osteopetrosis (marble bones, Albers-Schönberg disease), fibrous dysplasia of bone, " osteomata " in soft tissues (possibly akin to so-called *myositis ossificans progressiva*), vascular malformations (such as congenital arterio-venous aneurysms, and coarctation of the aorta), scleroderma, Meige's trophœdema (Milroy's disease), chondrodystrophy (achondroplasia), craniostenosis, neurofibromatosis (including local gigantism and local dwarfism), and tuberous sclerosis.

Clinical notes and some histological observations of a case of melorheostosis are reported.

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PHOSPHORUS POISONING WITH CORTICAL NECROSIS OF THE KIDNEY: A REPORT OF TWO FATAL CASES[1]

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THE purpose of this communication is to record two fatal cases of phosphorus poisoning occurring in siblings under the age of four years. The tragic death of these children emphasizes both the danger of yellow phosphorus as a poison, and the diagnostic problem presented because of the departure of these cases from the usual clinical picture.

Elementary phosphorus does not occur free in nature, being found usually in the form of a phosphate. Its isomeric form, red or amorphous phosphorus, is non-volatile, insoluble, not absorbed and non-toxic by mouth. Red phosphorus may contain 0·6% of yellow phosphorus and is therefore dangerous if taken in quantity. Yellow phosphorus is practically insoluble in water, but diffuses through water as a vapour and forms a dilute colloidal solution. It is soluble in fats and bile and is therefore absorbed from the gut. Although the commonest mode of introduction is by way of the gut, intoxication with phosphorus can occur through the skin and lungs. In adults the minimum lethal dose of phosphorus is between 50 and 100 milligrammes, or about one milligramme per pound of body weight; doses as low as 15 milligrammes have produced toxic symptoms. Reports of recovery after large doses of 200 milligrammes (Smith, 1938) and 400 milligrammes (Chretien, 1945) are recorded. Diaz-Rivera, Collazo, Pons and Torregrosa (1950) have shown that the size of the dose and the vehicle in which it is ingested are the most important features in determining mortality.

The source of phosphorus in cases of poisoning is mostly a vermin poison, which may contain from 1% to 4% of yellow phosphorus, sufficient to be recognized by its garlic-like odour and luminiscence in the dark.

The incidence of the disease has dwindled, because in many countries the use of yellow phosphorus has been prohibited in the manufacture of fireworks and matches. Reports from the United States of America of cases occurring after the ingestion of fireworks (Humphreys and Halpert, 1931) are not uncommon, and many text-books refer to the old-fashioned lucifer as a source of phosphorus poisoning. Before precautions were taken, both fireworks and matches were a source of danger to workers in the industry and to children, who might accidentally ingest articles containing the poison.

At one stage a survey in the United States of America revealed that some 5% of workers in the fireworks industry had some form of necrosis of the mandible (Wells, 1926).

A leading article in *The Medical Journal of Australia* (1929) contains the following statement:

> The problem has not been felt in Australia. The manufacture of lucifer matches in Australia is a comparatively recent development and as far as we are aware white or yellow phosphorus has not been used at any time, at all events on a large scale.

The most likely sources seem to be rat and roach poisons (Orr and Sager, 1950; Blumenthal and Lesser, 1938; McLean, Macdonald and Sullivan, 1929), which are available from a grocer's shop and are labelled "poison", but require no special conditions for purchase. The maker recommends that sandwiches be prepared containing the poison and left abroad for the destruction of rats.

Rubitsky and Myerson (1949) report 1457 subjects of poisoning admitted to the Boston City Hospital in a ten-year period, among whom there were 14 cases of phosphorus poisoning with a mortality rate of 50%, compared with a mortality rate of 6·2% for those who had ingested other substances. Diaz-Rivera *et alii* (1950) report a mortality rate of 48% in a group of 56 cases from Puerto Rico, where rat paste is a popular poison for intending suicides.

Two cases will now be reported, and details will be given of the post-mortem findings and the report from the Victorian Government Analyst. In conclusion, the lesson learnt from these cases together with the public health implications will be mentioned.

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CASE HISTORIES

CASE I.—The first child, a female, C.M., aged twenty months, was admitted to the Children's Hospital, Melbourne, on September 12, 1948. She was the second child of a healthy family living in a Melbourne suburb, and presented with a history of diarrhœa and vomiting present for the past five days. On the day preceding her admission to hospital the diarrhœa was abating, but vomiting had increased. No urine had been passed for over twenty-four hours.

The child presented as a drowsy, irritable, sick baby with a temperature of 36·1° C., a pulse rate of 120 per minute and a respiration rate of 28 per minute. The pulse rhythm was regular and the volume full. No abnormality was detected upon examination of the cardiovascular or respiratory systems. No mass or viscus was palpable upon examination of the abdomen, and the central nervous system was clear. A provisional diagnosis of gasto-enteritis was made. On the day after her admission to hospital the patient was vomiting and not tolerating a gastric drip administration of fluid. The diarrhœa had ceased, but the urine output was negligible. The child was not febrile, and signs of central nervous system involvement including drowsiness, involuntary movement of the eyes, twitching of the limbs and one convulsive seizure, were present.

A complete clinical examination was again made and revealed scattered coarse tracheal adventitiæ and rhonchi over the lung fields. No abnormality was detected in the central nervous system. There was some evidence of dehydration. The clinical summary indicated that the patient was admitted to hospital with gastro-enteritis, and since her admission the main features had been vomiting and diminution of urinary secretion. In spite of all attempts to maintain fluid balance, the child died two days after her admission to hospital.

A post-mortem examination revealed the following findings.

There were about 15 millilitres of clear serous fluid in the pericardial sac, but no further abnormality in the cardio-vascular system. A few small petechial hæmorrhages were present on the parietal pleura of both lungs anteriorly on the upper lobes. Some œdema of the lung tissue was noted ; beyond this examination of the respiratory tract revealed no abnormality.

The gastro-intestinal tract was the site of a severe inflammatory process, with mild involvement of the last few inches of the ileum and the caecum and intense catarrhal inflammation of the colon and rectum as far as the anal canal. The gut above the terminal portion of the ileum appeared normal, although the mucosa of the stomach was very congested and a few small superficial ulcers were present. The liver was normal in size and moderately pale. The biliary system was normal. The inflammatory process in the bowel involved the whole wall and its serous covering, so that the mesenteric attachments and the lymph nodes therein appeared œdematous. The pancreas and adrenal glands were normal. The spleen was a little enlarged and follicular hyperplasia was noted. The kidneys, though normal in size, upon removal of the capsules were found to have small hæmorrhagic areas deep in the cortex. In the cut surfaces there was a zone of hæmorrhagic discoloration, adjacent to the bases of the pyramids. The renal pelves, the ureters and the urinary bladder were normal.

No abnormality was detected in the cerebrum, brain stem, pons, cerebellum and medulla.

The appearance of the kidneys suggested a zone of necrosis in the cortex, similar to that illustrated by Trueta, Barclay, Daniel, Franklin and Prichard (1947) in their discussion on the pathological and clinical implications of the disturbance of intrarenal blood flow between cortex and medulla and in the kidney of rabbits subjected to the intravenous injections of staphylococcus toxin. One kidney therefore was perfused with normal saline at a pressure of 120 millimetres of mercury to remove blood, and this procedure was followed by the perfusion of the organ with a gelatin methylene blue mass. The result of this experiment showed that the area of apparently necrotic cortex failed to fill with blue mass, indicating damage and blocking of the vessels in this region. Previous experience of the injection of kidneys with this type of mass had resulted in satisfactory filling of the subcapsular cortex.

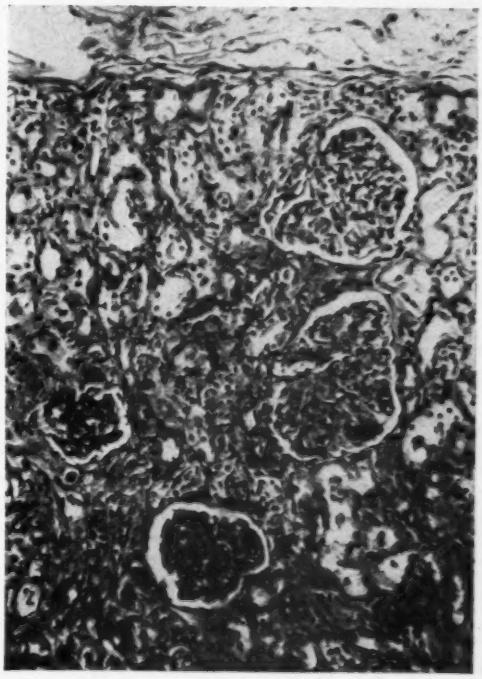

FIGURE I

Case I: Section of kidney, showing renal capsule at top, beneath which lies cortex with two glomeruli, within normal limits. Adjacent to this two severely damaged glomeruli are surrounded by degenerating tubules showing poor cellular differentiation. (Hæmatoxylin and eosin stain, × 265)

Histological examination of the kidney (Figure I) revealed gross degenerative changes in the tubules and glomeruli in a zone of the cortex between one and two low power fields in from the capsule. The

glomeruli were structureless and grossly congested, the epithelium of the tubules was confluent and degenerate, and there was considerable interstitial cellular infiltration with non-granular mononuclear cells in this region. This zone of degenerative change merged superficially

FIGURE II
Case I: Section of colonic mucosa showing extreme epithelial denudation and degeneration. (Hæmatoxylin and eosin, × 265)

and deeply into the areas of kidney substance approaching normality. No abnormality was seen in the blood vessels outside the affected zone. In tubules deeper in the medulla, eosinophilic amorphous material was present in their lumina.

Microscopic examination of the lungs revealed pulmonary œdema, congestion and mild bronchitis. In the colon (Figure II) there were extensive changes involving all layers from the mucosa to the serosa. The liver (Figure III) though showing some evidence of glycogen-rich hypocytoplasmic liver cells in the vicinity of the portal tracts, showed no evidence of fat accumulation.

Organs from this autopsy were sent to the Victorian Government Analyst, who detected yellow phosphorus in the stomach washings, liver, kidneys and stomach wall of this child.

CASE II.—The second patient, L.M., a boy, aged three years, was admitted to hospital on the day of his sister's death. He had been well until five days before, when he complained of diarrhœa, to the extent of the passage of four or five very loose stools per day. Vomiting commenced on the following day, and the diarrhœa gradually decreased.

On examination, the child presented as a well-nourished boy, somewhat drowsy, but cooperative. The temperature was 37·1° C., the pulse rate was 122 per minute, and respiration rate 22 per minute. No abnormality was detected upon examination of the cardio-vascular and respiratory systems. It was thought that there was some rigidity of the muscles of the right upper quadrant of the abdomen, and that the liver was palpable two fingers' breadth below the right costal margin. Nine hours after the child's admission to hospital no urine had been passed. The proctoscopic examination at this time revealed hyperæmia of the rectal mucosa. Culture from a swab taken at this time yielded no pathogenic organisms. During the child's five-day stay in hospital his clinical condition deteriorated, with occasional vomiting and convulsions. His urinary output was minimal and his blood urea level rose to over 200 milligrammes per 100 millilitres. In spite of treatment designed to maintain adequate hydration and the administration of BAL, the child died ten days after the onset of symptoms.

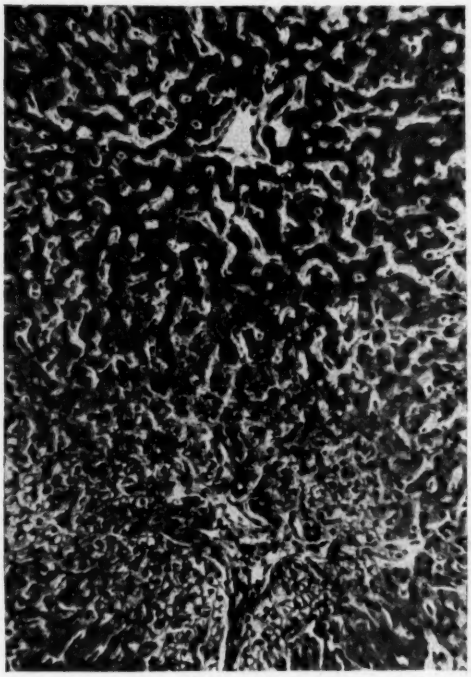

FIGURE III
Case I: Section of liver, showing cell vacuolation surrounding a portal tract. (Hæmatoxylin and eosin, × 265)

In view of the circumstances surrounding the death of this patient's sister and the Government Analyst's report, it was considered that phosphorus poisoning was the cause of the second child's death. The case was reported to the Melbourne City Coroner, who ordered an autopsy. The examination was performed by Dr. K. M. Bowden, to whom I am indebted for the following findings.

Examination of the lungs revealed moderately gross pulmonary œdema; the liver was somewhat increased in size but otherwise normal. Multiple hæmorrhages were present throughout the entire cortical substance of the kidneys. In the cut surfaces the appearance was similar to that already described in Case I. Histological examination of the kidney

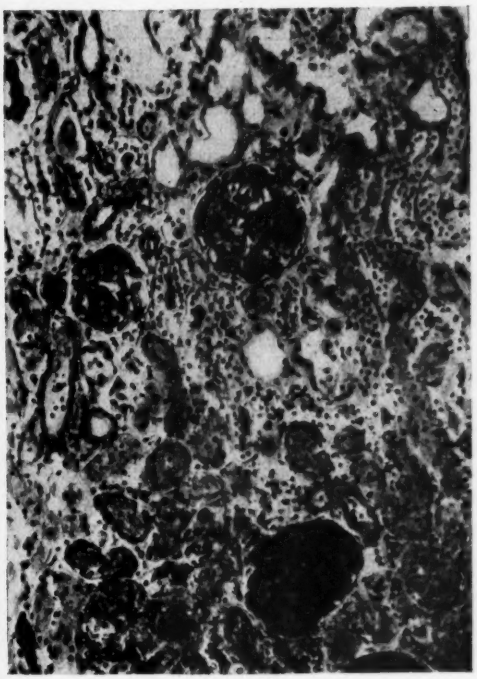

FIGURE IV

Case II: Section of kidney, showing gross glomerular degeneration; there is also loss of outline of surrounding tubular cells. (Hæmatoxylin and eosin, × 265)

(Figure IV) revealed an appearance almost identical with that described in Case I. Yellow phosphorus was detected by the Government Analyst in the liver and kidneys of this child.

DISCUSSION

Rubitsky and Myerson (1949) divide the symptoms of phosphorus poisoning into three stages. Within six to eight hours of ingestion abdominal pain, vomiting and shock usually occur, whilst diarrhœa occurs in 35% of cases. Within three days of ingestion there is a period of apparent improvement lasting for as long as ten days. Finally there is a stage of systemic toxæmia, with a recurrence of vomiting, abdominal tenderness, enlargement of the liver, jaundice and oliguria. Involvement of the central nervous system is evident by the occurrence of coma, delirium and convulsions. These authors emphasize that during this stage liver damage is profound and predominant. The two cases described above illustrate some of the characteristic features of phosphorus poisoning—vomiting, diarrhœa and oliguria. Diarrhœa was a prominent feature of both cases and the extreme severity of the bowel lesion in Case I is worthy of note. The gastro-intestinal symptoms were so prominent that acute infective enteritis was seriously considered, in spite of the absence of significant pyrexia. The oliguria, which in both cases was nearing anuria, is explained by the pathological changes in the kidneys. I am unable to discover reports of so clear an example of cortical necrosis in phosphorus poisoning. The oliguria in most cases seems to be accounted for by shock, peripheral circulatory failure, and the local effect of the poison on the renal tubules. The occurrence of this lesion in these cases is of interest in the light of the ætiology of cortical necrosis suggested by Trueta *et alii* (1947). McLean *et alii* (1929) described a case of fatal phosphorus poisoning in a baby, aged eighteen months, in which there were renal congestion and degeneration of epithelial cells of the cortex, but oliguria was not a predominant feature of the child's illness.

Although commercial vermin poisons containing yellow phosphorus are readily available in Australia, phosphorus poisoning is a rare disease in this country, no case having been reported in *The Medical Journal of Australia* in the last thirty-two years.

Investigations by the Victorian Police Department revealed that in the neighbourhood of the home of the two children whose cases are reported above, rat baits containing phosphorus had been distributed. Two days later all the fowls in a nearby pen were discovered dead, although the baits had not been laid in the fowl pen.

The tragedy of these two children emphasizes the desirability of abolishing domestic vermin poisons that contain substances injurious to humans, or of stricter supervision of their distribution.

ACKNOWLEDGEMENTS

I am indebted to Dr. Howard Williams, of the Clinical Research Unit, for permission to use this clinical material. Dr. K. M. Bowden kindly supplied the post-mortem report of the second case. The photographs were prepared by Mr. E. Matthei, of the Faculty Workshops, University of Melbourne.

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THE VARIATION FROM DAY TO DAY IN THE HÆMOGLOBIN VALUE OF YOUNG WOMEN[1]

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VARIATION of the blood hæmoglobin concentration from day to day is shown in this paper to be greater than can be attributed to experimental error, diurnal variations or environmental change. The importance of this variation is that difficulties may arise when a clinical diagnosis of mild anæmia is made on a single examination of the blood, or when the response of an anæmic patient is being assessed by repeated blood counts.

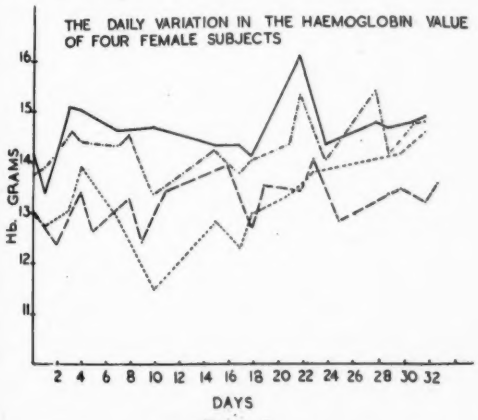

FIGURE I.

The variations of the hæmoglobin values from day to day in four healthy young women.

METHODS

Blood samples were collected from 26 female volunteers (nurses, assistants in nursing and clerks) on four occasions each week for four successive weeks. The blood, collected by venepuncture at the same time of day on every occasion, was mixed with crystals of ammonium and potassium oxalate, and the hæmoglobin concentration was determined by a photo-electric hæmoglobinometer. The apparatus, method of calibration and technique of measurement will be described elsewhere (Walsh, Arnold, Lancaster, Coote and Cotter, 1953).

[1] Received for publication on January 16, 1953.

RESULTS

A total of 395 estimations were performed on the 26 volunteers. The difference between the highest and the lowest values for each subject ranged from 0·8 to 3·0 grammes with a mean of 1·75 grammes. The difference was greater than 2·0 grammes in seven subjects. Expressed in terms of the mean of all tests performed on the subject, the difference varied between 7·3% and 22·7%. The hæmoglobin values of four subjects are plotted in Figure I.

The hæmoglobin values for fifteen days before and after the onset of menstruation are recorded in Table I. The full series of estimations was not made on some of the subjects, and results outside a range of fifteen days from the onset of menstruation have not been included in Table I, or used in the calculations of the regressions before and after menstruation.

Statistical Analysis

In only 17 subjects was the complete series of 16 readings obtained. A first analysis of these figures is given in Table II, where analysis of variance is used to assess the variation between counts and to apportion this variation to its several causes. It may first be noted that differences in the mean level of hæmoglobin values are naturally to be expected between different subjects. This variation is taken out in Line A of Table II and does not come into

TABLE II.

The Analysis of the Sources of Variation: 17 Subjects with 16 Hæmoglobin Estimations.

Source of Variation.	Degrees of Freedom.	Sums of Squares.	Mean Square.
A. Differences between subjects	16	170·573	10·661
B. Differences between days	15	7·166	0·478
C. Interaction (error or residual)	240	54·973	0·229
Total	271	232·712	—

TABLE I.

The Hæmoglobin Values (Grammes per 100 Millilitres of Blood) of Healthy Young Women.

Subject.	Age of Subject. (Years.)	Days Before Commencement of Menstruation.															Days After Commencement of Menstruation.														
		−15	−14	−13	−12	−11	−10	−9	−8	−7	−6	−5	−4	−3	−2	−1	0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	+13	+14	+15
1	40	16·5	15·4			16·5			15·6					16·5		16·2	16·8			16·3	16·0		16·8				16·5	16·4		16·5	16·8	
2	22	14·5	14·8			13·8			14·5					14·9		14·3	14·9			13·5	14·1		15·5				13·5	14·6		14·5	16·4	
3	22			13·0	12·9			13·1	13·0		14·3				12·7	13·4		13·5	14·4												
4	22							15·5	15·7		15·0	15·8			15·2	15·0		15·4					15·3		14·8	15·2			14·8	14·7		15·3
5	20	14·0	15·3	14·8			15·0			15·3					14·2		14·3	14·3			14·4	15·4		14·0				14·7	14·9		14·4	14·8
6	18	13·0	12·8		13·1	13·9			12·9			11·5				12·8			12·3	13·0			13·4	13·4		13·8					
7	38	14·2	15·0			15·0	14·4		14·8					14·6		14·3	14·4			14·2	14·8		14·3				14·2	14·7		15·4	15·0	
8	20					15·2		14·3		15·0	14·3			14·3			14·0					14·5		13·8	14·7			14·8	15·2		15·1	
9	22											13·8	14·0		13·9	14·4					14·2		14·3								
10	19					14·5	14·6		15·2	15·3			13·9	14·4		14·2					14·9		15·0	14·4			14·7	14·9		14·6		
11	21							13·4	13·4		13·1	13·5			13·1			12·2							13·4	13·2			13·4	13·3		13·8
12	23	13·9			13·9			13·2					14·0		13·4	13·3				12·6		12·9				13·2	13·7		13·4	13·3		
13	32			13·8	13·9		14·6	14·4			14·3	14·5		13·4					14·2		13·8	14·0			14·3	15·3		14·0			15·3
14	—														14·3	13·9		15·2	15·0			14·6			14·6					14·3		14·3
15	20										14·4	14·7	14·9	14·6				14·6		14·7					15·0			14·3	15·0		14·7	14·1
16	21											13·2	13·1		12·7	12·8			13·4	12·7		12·4						13·4		13·7	13·4	
17	30										12·6	13·2		13·5	13·8			13·0	13·2		12·3				13·2		13·4	13·1			13·7
18	20															10·9		11·2	11·3			10·3	10·6		10·5			11·3			11·2
19	36													13·1		12·4		13·4	12·8			13·3			13·4				13·9		12·7
20	23																	14·1	14·0		13·8	14·0			14·2	13·9		14·2			
21	23																13·7	14·4		14·9	15·3			14·7	14·7		14·5				14·4
22	21			13·2		13·2	12·7			13·1	13·1		13·0				12·9	12·8		13·1	13·9										
23	32		13·7					14·6		14·2	14·5			14·2	14·3					13·1	13·8		13·5	13·7							
24	21			15·0		14·3	14·3			14·6	15·6		14·0				13·9	14·1		14·0	14·4										
25	27·			14·3					15·3		14·2	14·1			14·5	14·2		14·3				14·8	15·3								
26	30	14·6			14·7	15·2		15·0				14·7	14·5		15·0	15·0			14·6	13·4											
Mean	—	14·4	14·5	14·1	13·7	14·6	14·3	14·2	14·5	14·6	14·0	13·9	13·9	14·4	13·9	13·9	14·2	13·7	13·5	13·7	14·3	13·6	14·2	14·0	13·9	14·0	14·3	14·7	13·7	14·5	15·2	14·0

the subsequent analysis. The remaining variation is divided into two parts—B, the differences between days, and C, the interaction term. In part B are included systematic disturbances due to the reading of the hæmoglobinometer and systematic changes, seasonal for example, in the hæmoglobin values of the subjects. Part C is the interaction term. It is a measure of the mean square of the differences between hæmoglobin values of each subject less an amount due to the differences between days.

The variance due to days is more than twice that due to the interaction. This variance ratio is significant at the 5% level. Its cause is difficult to assess. It appears to be partly due to a slight increase in the average hæmoglobin value. The sums of the squares in line B may be broken into two parts, that due to regression and a remainder. The ratio of the mean squares of these two parts is 1·736, which is significant at the 5% level. This slight rise cannot be due to a summation of cyclical effects of the different women, since the commencement of the series is random with regard to the menstrual cycle of the subjects. It is of some interest to study the mean square of the interaction or error term more closely—that is, line C of Table II. This mean square, 0·229, is a measure of variation of individual subjects from day to day, of errors of collection, of errors of estimation and chance differences. It is more than twice the mean square of the error term, 0·110, found when repeated collections were made on the same subjects on the same day (Walsh *et alii*, 1953). The standard deviations are approximately 0·33 gramme for sets of estimations on the same day and 0·48 gramme per 100 millilitres when estimations are made on different days.

In a second analysis of the data of Table I, the linear regressions have been computed for all series after the onset having two or more terms. The sum of squares due to regression is significantly large. For the days after menstruation the slope is positive for most subjects—that is, the hæmoglobin values are increasing. In 18 the hæmoglobin values are increasing, in seven they are falling, and in one subject with only two readings there is no slope. Of those subjects with six, seven or eight readings, regression coefficients were, in order of magnitude, +0·11, +0·10, +0·08, +0·08, +0·07, +0·06, +0·04, +0·04, +0·02, +0·01, +0·01, −0·02, −0·02, −0·03, −0·03, −0·06, −0·06, −0·12 gramme of hæmoglobin per 100 millilitres of blood per day. Of these subjects 11 had positive slopes (that is, the hæmoglobin value was increasing) and seven had negative slopes.

For the days before menstruation the slope is negative in 13 cases, positive in 19 cases and zero in one case. Of those subjects with six, seven or eight readings, the regression coefficients were, in order of magnitude, +0·07, +0·07, +0·06, +0·06, +0·03, +0·03, +0·01, −0·02, −0·05, −0·07, −0·10, −0·11, −0·11, −0·13, −0·17; of these seven slopes were positive and eight were negative.

When they could be compared, the signs of the two slopes before and after menstruation agreed in eight and differed in 14 cases. They would tend to differ if there had been a rise or fall in hæmoglobin values at the time of menstruation. Of 13 subjects with a fall before, nine showed a rise after menstruation.

DISCUSSION

The variation of the hæmoglobin value from day to day has been found to be considerably greater than that which occurs during any one day. With the same technique of measurement, the latter was previously found (Walsh *et alii*, 1953) to vary between 0·3 and 1·7 grammes in a series of five readings in each of 34 subjects. The day-to-day variation is of sufficient magnitude to lead to erroneous diagnoses of mild anæmia and to fallacious assessments of therapy. The results have been obtained on healthy ambulatory subjects, but there is no information concerning either the diurnal or the day-to-day variations in bed patients. Nevertheless the desirability of repeating blood examinations on patients thought to be suffering from mild anæmia is evident.

It has been shown above that the standard deviation of the hæmoglobin values is greater when the estimations are made on different days than when they are made at different times on the same day. The importance of this can be appreciated with the aid of statistical theory. From tables of the range for sets of 16 observations, it is found that the range exceeds 4·80 times the standard deviation in 5% of the sets. With a standard deviation of 0·47 gramme the range may be expected to be greater than 2·3 grammes *per centum* in 5% of the cases. The three largest ranges in the present series may be attributed to such chance variations rather than to cyclical changes related to menstruation.

The mechanism by which the day-to-day variations are produced has not been investigated. They may be the results of variations in the plasma volume and of the distribution of body water generally. However, there is

evidence (Gibson *et alii*, 1946) that the proportion of red cells to plasma varies in different regions of the body, and that this relationship is subject to changes, possibly according to the functional activity of the parts. The variations of the hæmoglobin value from day to day may result from changes in the concentration of red cells in the blood of the region under examination without alteration either of the total plasma or red cell volumes.

It has been suggested (Greenhill and Freed, 1941) that hydræmia occurs preceding the onset of menstruation. This has been demonstrated by an increase in body weight at this time. Our results are consistent with a fall in the hæmoglobin values about this time in some but not in all subjects. It is suggested that any future investigation of this problem should include determinations of body weight as well as of hæmoglobin value.

The analysis shown in Table II suggests that there may be some systematic disturbing factor, because there is a small but significant increase in the mean values each day during the experiment. This is unlikely to be due to changes in the instrument, because samples of known hæmoglobin value were tested before and after the experiment without detectable change in calibration. On the other hand, the increase could represent a seasonal variation. It has been shown previously (Walsh *et alii*, 1953) that the mean value of comparable subjects is higher in winter than in summer, and the experiment reported in this paper was commenced on warm days and completed when the average temperature had decreased by several degrees.

SUMMARY

In healthy young women the hæmoglobin value of venous blood was found to vary from day to day by as much as 3·0 grammes per 100 millilitres of blood. This variation is due either to fluctuations in the plasma volume or to redistribution of the plasma-red cell ratio in different regions of the body. Its importance is obvious in relation to the diagnosis of mild anæmia, and in the assessment of therapy. The findings are consistent with the existence in some subjects of hæmodilution preceding the onset of menstruation.

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THE FUNCTION OF THE ADRENAL CORTEX IN RHEUMATIC FEVER [1]

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WITH the discovery of ACTH and cortisone and their ability to reverse dramatically the clinical manifestations of the rheumatic process (Massel, 1950) a new stimulus has been given to link the presumed allergic reaction in rheumatic fever with aberration in endocrine function of the host.

Although our present understanding of the action of cortisone and ACTH has hardly progressed beyond the stage of superficial description, there are indications that resistance to allergic reactions depends on an intact adrenal cortex (Dougherty, 1950). Furthermore, there has now accumulated extensive evidence that the delayed type of allergic reaction is inhibited to some extent by ACTH and cortisone (Berthrong, Rich and Griffith, 1950; Long and Favour, 1950; Rich, Berthrong and Bennet, 1950; Govier and Feenstra, 1951). Whilst the results of these investigators await confirmation, they suggest that depression of adrenal or pituitary function may contribute to the manifestations of the delayed type of allergic reaction (Pickering, 1952).

In view of the therapeutic effects of cortisone and ACTH in rheumatic fever, a disease long considered to share many of the features of the delayed type of allergic reaction, it was decided to investigate the function of the adrenal cortex in patients suffering from acute rheumatic fever with the view to determining whether the presumed allergic reaction in that disease is associated with depression of adrenocortical function.

Among the many metabolic changes observed with the use of ACTH, the decrease in circulating eosinophile cells is among the most sensitive and easily measured (Lewis, 1949). Thorn and associates (1948) have described a test for adrenal cortical insufficiency based on the eosinopenic response to ACTH. In persons with defective function of the adrenal cortex there was little or no decrease in circulating eosinophile cells, four hours after a single 25 milligrammes dose of ACTH. In subjects known to have normal adrenal cortices there was a 50% or greater decrease in the number of circulating eosinophile cells. The administration of adrenaline or ephedrine (Hume, 1949; Recant, Hume, Forsham and Thorn, 1950), by causing the liberation of endogenous ACTH, will produce a similar reduction in the number of circulating eosinophile cells, provided both pituitary and adrenocortical activities are adequate.

The response of circulating eosinophile cells to these substances offers thus a convenient way of assessing adrenocortical function.

EXPERIMENTAL INVESTIGATION

The effect of ACTH, adrenaline and ephedrine on the circulating eosinophile cells in rheumatic fever was studied.

Method of Counting Eosinophile Cells

The method of counting eosinophile cells has been described previously (Wiener, 1952*b*). The eosinophile cells were counted in a counting chamber, after having been stained with a special diluting fluid of the following composition: propylene glycol 50 millilitres, 1% aqueous phloxine solution 19 millilitres, 10% aqueous sodium carbonate solution two millilitres, distilled water to 100 millilitres.

Choice of Patients and Method of Performing Test

The age of the patients who were investigated as in-patients at the Children's Hospital, Melbourne, ranged between seven and thirteen years. They were suffering from the major manifestations of rheumatic fever including chorea. The diagnosis was confirmed after careful evaluation of the history, of the results of physical examination and of any special investigations, such as the erythrocyte sedimentation rate, antistreptolysin titre, leucocyte count and the electrocardiographic findings. Any doubtful cases were excluded. All the patients were receiving salicylate medication.

From a freely bleeding finger puncture, blood was collected into four white cell pipettes. In two of these the blood was diluted 1 : 10

[1] Received for publication on November 3, 1952.

and 1 : 20 with the eosinophile and white cell diluting fluids respectively. Two cells of a Fuchs-Rosenthal chamber were filled from each of the two pipettes for eosinophile cell counts. The other two pipettes were used to fill the ordinary chamber for white cell counts.

Blood was collected at 8 a.m. for an initial cell count, and 10 milligrammes of ACTH were injected intramuscularly. Into another group of patients 0·3 milligramme of adrenaline hydrochloride was injected subcutaneously. The third group of patients was given 30 milligrammes and 60 milligrammes of ephedrine sulphate orally.

Four hours later blood was collected for the second cell counts.

Since Rud (1947) has shown that the eosinophile level is subject to diurnal variations, there being a mid-morning drop of about 20% from the 8 a.m. level, the eosinophile cells were counted in blood from five patients at 8 a.m. and 12 mid-day, one day prior to the administration of ACTH.

Results

Table I shows (Cases I to V and IX) that under constant conditions, such as occur in a hospital,

TABLE I

Effect of Ten Milligrammes of ACTH on the Circulating Eosinophile Cells and Total Leucocytes in Rheumatic Fever

Case Number	Eosinophile Cells per Cubic Millimetre on Day Before Administration of ACTH		Eosinophile Cells and Leucocytes per Cubic Millimetre Before and After Injection of 10 Milligrammes of ACTH[1]		Percentage Fall in Eosinophile Cells
	8 a.m.	12 Noon to 1 p.m.	8 a.m.	12 Noon to 1 p.m.	
I	315	280	290 12,400	115 12,680	60
II	400	390	325 12,740	150 12,840	54
III	—	430	370 6,680	140 7,320	62
IV	374	364	350 16,640	215 15,400	38
V	355	195	375 12,360	216 13,610	42
VI	—	—	556 7,760	204 6,720	63
VII	—	—	500 11,520	336 10,380	49
VIII	—	—	204 11,900	126 12,880	38
IX	268	271	291 14,520	165 15,690	43
X	—	—	423 12,680	294 11,400	30

[1] Upper line, eosinophile cells; lower line, leucocytes.

the level of circulating eosinophile cells shows little change. The child in Case V was crying with severe precordial pain when blood was collected at 12 mid-day on the day prior to the administration of ACTH. The non-specific stress thereby produced may account for the reduction of the eosinophile cells which occurred. By the use of the criteria of significance as established previously (Wiener, 1952*b*), it can by seen from Table I that a significant reduction in the number of circulating eosinophile cells occurred in every case after the administration of 10 milligrammes of ACTH.

TABLE II

Eosinophile Cell Counts Before and Four Hours After the Administration of 0·3 Milligramme of Adrenaline to Rheumatic Patients

Case Number	Eosinophile Cells per Cubic Millimetre		Percentage Fall
	Before	After	
I	281	95	66
II	264	112	59
III	168	58	66
IV	622	175	72
V	344	77	78
VI	328	123	62
VII	161	74	54

A similar effect was obtained with 0·3 milligramme of adrenaline (Table II).

TABLE III

The Effect of 60 Milligrammes of Ephedrine Sulphate on the Circulating Eosinophile Cells in Rheumatic Fever

Case Number	Eosinophile Cells per Cubic Millimetre		Percentage Reduction
	Before	Four Hours After	
I	540	235	56
II	193	43	78
III	184	35	90
IV	225	67	70
V	352	196	44
VI	526	270	49

There also occurred a significant reduction in the number of circulating eosinophile cells

TABLE IV

The Effect of 30 Milligrammes of Ephedrine Sulphate on the Circulating Eosinophile Cells in Rheumatic Fever

Case Number	Eosinophile Cells per Cubic Millimetre		Percentage Change
	Before	Four Hours After	
I	343	284	−17
II	325	225	−39
III	425	380	−11
IV	176	131	−26
V	79	100	+27
VI	241	188	−22

four hours after the oral administration of 60 milligrammes of ephedrine sulphate, in five out

of six patients with rheumatic fever (Table III). However, a dose of 30 milligrammes of ephedrine sulphate was ineffective in reducing the number of eosinophile cells significantly (Table IV).

DISCUSSION

It appears that the function of the adrenal cortex, measured in terms of its ability to reduce the number of circulating eosinophile cells under the influence of ACTH, is not impaired during an attack of rheumatic fever. To judge by the eosinopenic effect obtained with adrenaline and adequate amounts of ephedrine, there also appears to exist a normal pituitary - adrenocortical relationship in rheumatic fever. A single injection of 10 milligrammes of ACTH was effective in every case in producing significant eosinopenia. Massel *et alii* (1950) similarly conclude from studies on the clinical effects of ACTH in children with rheumatic fever that the minimal effective individual dose may be between five and 10 milligrammes.

Except for conditions of frank adrenal cortical insufficiency as occurs in Addison's disease, in panhypopituitarism or after adrenalectomy, there is so far no convincing evidence that those conditions which are favourably modified by ACTH or cortisone are actually associated with deficiency of adrenocortical secretion (Sprague, 1951). The result of the present investigation suggests that adrenal cortical function is not depressed in rheumatic fever.

The relatively large amounts of ACTH or cortisone that must be administered before a favourable clinical effect can be achieved would indicate that the effectiveness of these substances depends more on the establishment of a state of hormonal excess in the tissues than on the mere substitution of hormones withheld by a sluggish adrenal cortex.

From the numerous reports of favourable modifications of the course of a variety of allergic diseases, it appears that the allergic process is blocked at some point by cortisone and ACTH without interference with the antigen-antibody reaction or with the consequent liberation of any noxious substance (Sprague, 1951). The effect of ACTH and cortisone in ameliorating the clinical manifestations of allergic conditions may be brought about by their action on the tissue cells, with the production of what may be called " cellular anæsthesia " to whatever the noxious agent may be.

Concerning the fate of the circulating eosinophile cells after the administration of eosinopenic drugs, hardly anything is known. The work of Speirs and Meyer (1949) indicates that these cells are not stored temporarily in some organ. It has also been observed that the return of the level of circulating eosinophile cells is accompanied by a corresponding increase in bone marrow activity (Durgin and Meyer, 1951). It is not impossible that the thick coarse granules of the eosinophile cell contain some chemical substance which is liberated under the influence of ACTH. However, when leucocytes from normal subjects were incubated with ACTH and adrenal cortical extract from the rabbit, no reduction in the number of eosinophile cells occurred *in vitro* (Wiener, 1952*a*). When we know the function of the eosinophile cells, we may understand what happens to them under the influence of ACTH.

It appears from Tables I to IV that in rheumatic fever the level of circulating eosinophile cells is somewhat higher than the 250 cells per cubic millimetre considered by Discombe (1946) to be the upper limit of normality. This increase in the number of circulating eosinophile cells may possibly be considered as yet another link in the long chain of indirect findings favouring an allergic process in this disease.

SUMMARY

1. The effect of ACTH, adrenaline and ephedrine on the circulating eosinophile cells in rheumatic fever has been studied.

2. Ten milligrammes of ACTH, 0·3 milligramme of adrenaline and 60 milligrammes of ephedrine were effective in significantly reducing the number of circulating eosinophile cells in children with rheumatic fever.

3. The adequate eosinopenic effect obtained suggests that adrenocortical function is not impaired in rheumatic fever.

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